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NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
NEWS  2          "Ask CAS" for self-help around the clock
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                 and searchable
NEWS  4  JAN 27  A new search aid, the Company Name Thesaurus, available in
                 CA/CAplus
NEWS  5  FEB 05  German (DE) application and patent publication number format
                 changes
NEWS  6  MAR 03  MEDLINE and LMEDLINE reloaded
NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
NEWS  8  MAR 03  FRANCEPAT now available on STN
NEWS  9  MAR 29  Pharmaceutical Substances (PS) now available on STN
NEWS 10  MAR 29  WPIFV now available on STN
NEWS 11  MAR 29  No connect hour charges in WPIFV until May 1, 2004
NEWS 12  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS 13  APR 26  PROMT: New display field available
NEWS 14  APR 26  IFIPAT/IFIUDB/IFICDB: New super search and display field
                 available
NEWS 15  APR 26  LITALERT now available on STN
NEWS 16  APR 27  NLDB: New search and display fields available

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              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004

=> file uspatful
COST IN U.S. DOLLARS                                  SINCE FILE     TOTAL
                                                           ENTRY   SESSION
FULL ESTIMATED COST                                         0.21      0.21

FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 29 Apr 2004 (20040429/PD)
FILE LAST UPDATED: 29 Apr 2004 (20040429/ED)
HIGHEST GRANTED PATENT NUMBER: US6728968
HIGHEST APPLICATION PUBLICATION NUMBER: US2004083524
CA INDEXING IS CURRENT THROUGH 29 Apr 2004 (20040429/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 29 Apr 2004 (20040429/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the      <<<
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>>>  original, i.e., the earliest published granted patents or          <<<
>>>  applications.  USPAT2 contains full text of the latest US           <<<
>>>  publications, starting in 2001, for the inventions covered in       <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original       <<<
>>>  published document but also a list of any subsequent                <<<
>>>  publications.  The publication number, patent kind code, and        <<<
>>>  publication date for all the US publications for an invention       <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL     <<<
>>>  records and may be searched in standard search fields, e.g., /PN,   <<<
>>>  /PK, etc.                                                           <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together          <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to            <<<
>>>  enter this cluster.                                                 <<<
>>>                                                                      <<<
>>>  Use USPATALL when searching terms such as patent assignees,         <<<
>>>  classifications, or claims, that may potentially change from        <<<
>>>  the earliest to the latest publication.                             <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> e schwartz olivier/in
E1            2      SCHWARTZ NORMAN LARRY/IN
E2            1      SCHWARTZ NORMAN STEPHEN/IN
E3            2 --> SCHWARTZ OLIVIER/IN
E4            1      SCHWARTZ OSCAR H/IN
E5            9      SCHWARTZ OSTEN/IN
E6            1      SCHWARTZ OTTO H/IN
E7            1      SCHWARTZ P CHRISTOPHER/IN
E8            1      SCHWARTZ PATRICIA A/IN
E9            2      SCHWARTZ PATRICIA ANN/IN
E10          16      SCHWARTZ PAUL/IN
E11          19      SCHWARTZ PAUL A/IN
E12           7      SCHWARTZ PAUL D/IN

=> s e3
L1            2 "SCHWARTZ OLIVIER"/IN

=> d l1,ti,1-2

L1   ANSWER 1 OF 2  USPATFULL on STN
TI     MHC-I-restricted presentation of HIV-1 virion antigens without viral
       replication. Application to the stimulation of CTL and vaccination in
       vivo; analysis of vaccinating composition in vitro

L1   ANSWER 2 OF 2  USPATFULL on STN
TI     Glycosyl phospholipid derivatives of nucleosides and their use as
       medicines


=> d l1,cbib,ab,clm

L1   ANSWER 1 OF 2  USPATFULL on STN
2002:307564 MHC-I-restricted presentation of HIV-1 virion antigens without
    viral replication. Application to the stimulation of CTL and vaccination in
    vivo; analysis of vaccinating composition in vitro.
    Schwartz, Olivier, Paris, FRANCE
    Buseyne, Florence, Paris, FRANCE
    Marsac, Delphine, Paris, FRANCE
    Michel, Marie-Louise, Paris, FRANCE
    Riviere, Yves, Paris, FRANCE
    Heard, Jean-Michel, Paris, FRANCE
    US 2002172683 A1 20021121
    APPLICATION: US 2002-83678  A1  20020227 (10)
    PRIORITY: US 2001-271432P  20010227 (60)
```

DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Dendritic cells and macrophages can process extracellular antigens for presentation by MHC-I molecules. HIV-1 epitopes derived from incoming virions are presented through the exogenous MHC-I pathway in primary human dendritic cells, and to a lower extent in macrophages, leading to cytotoxic T lymphocyte activation in the absence of viral protein neosynthesis. Exogenous antigen presentation required adequate virus-receptor interactions and fusion of viral and cellular membranes. These results provide new insights about how anti-HIV cytotoxic T lymphocytes can be activated and are useful for anti-HIV vaccine design.

CLM What is claimed is:

1. An immunogenic composition capable of inducing a cytotoxic response in vitro or in vivo against a viral disease through a MHC-1 restricted exogenous antigen presentation pathway without requiring viral replication, containing at least one of the compounds: (A) a first plasmid containing a polynucleotide corresponding to the entire or a part of the viral genome and a second plasmid comprising in an insert containing a polynucleotide coding for a viral envelope (a part of the envelope or a surface protein) and being under the control of a promoter, said plasmids being selected for their fusogenic properties when binding to antigen presentation cells, and for inducing a cytotoxic response through a MHC-1 restricted exogenous antigen presentation pathway; (B) a plasmid comprising a polynucleotide coding for the entire or a part of the virus genome and contains an insert containing a polynucleotide coding for a viral envelope (or a part of the envelope or a surface protein), and being under the control of a promoter said plasmid expressing viral particles being selected for their fusogenic non-replicative properties, and for inducing a cytotoxic response afer a CMH-2 restricted exogenous antigen presentation pathway; (C) a virus with intact fusogenic capacities, but whose infectious capacities have been inactivated or attenuated; and (D) viral particles obtained by the purification of a cell culture supernatant.

2. An immunogenic composition according to claim 1 wherein the viral particles obtained by the purification of a cell culture supernatant are prepared by transfecting producing cells (for example, HeLa, 293) with the plasmids according to claim 1 and purifying the supernatant, or by infecting antigen presenting cells with an HIV virus, purifying the supernatant, and inactivating or attenuating the infectious capacity of the virus.

3. A vaccinating composition containing the immunogenic composition according to claim 2 in association with a pharmaceutically acceptable vehicle.

4. A vaccinating composition containing the immunogenic composition according to claim 2 in association with another vaccine.

5. A vaccinating composition containing the immunogenic composition according to claim 2 wherein the composition is obtained by the process of claim 16.

6. A process of treatment of a eukaryotic host suffering from a viral pathology comprising administering a plasmid comprising a polynucleotide coding for the entire or a part of the virus genome and containing an insert containing a polynucleotide coding for a viral envelope (or a part of the envelope or a surface protein), and being under the control of a promoter, said plasmid expressing viral particles being selected for its fusogenic, non-replicative properties, and for inducing a cytotoxic response after a CMH-1 restricted exogenous antigen presentation pathway.

7. A process of treatment of a eukaryotic host suffering from a viral pathology comprising coadministering a first plasmid comprising the entire or a part of the virus genome and a second plasmid comprising an

insert containing a polynucleotide coding for a viral envelope (a part of the envelope or a surface protein) and being under the control of a promoter, said plasmid being selected for its fusogenic properties, and for inducing a cytotoxic response after an exogenous antigen presentation which is MHC-1 restricted.

8. A process of treatment according to claim 6 or 7, wherein the virus is an human or animal retrovirus.

9. A process of treatment according to claim 6 or 7, wherein the virus is HIV-1, HIV-2, SIV, FeLV, or FIV.

10. A process of treatment according to claim 6 or 7, wherein that the host is a mammal.

11. A process of treatment according to claim 6 or 7, wherein the host is a mouse.

12. A process of stimulation in vivo of cytotoxic lymphocytes through an MHC-1 restricted exogenous antigen presentation pathway without requiring viral replication, comprising: (A) administration of the plasmids contained in the immunogenic composition according to claim 1 or 2 to the host according to claim 10; (B) optionally the cytotoxic T cells obtained after the step A above are tested in a cytotoxic test comprising: (i) the incubation of an organ or a biologic fluid of the host containing cytotoxic T cells of the host with a synthetic peptide which sequence is encoded by a viral genome contained partly in the first or the second plasmid; or (ii) the use of target cells with the same HLA haplotype as the host or a compatible HLA haplotype, said target cell being incubated with a synthetic peptide which sequence is a part of the sequence of an HIV-genome.

13. A process of stimulation in vivo of cytotoxic lymphocytes through an MHC-1 restricted exogenous antigen presentation pathway without requiring viral replication, comprising: (A) administration of viral particles obtained by supernatant purification according to claim 2; (B) optionally the cytotoxic T cells obtained after step A above are tested in a cytotoxic test comprising: (i) the incubating of an organ or a biologic fluid of the host containing cytotoxic T cells of the host with a synthetic peptide which sequence is encoded by the genome contained partly in the first or the second plasmid; or (ii) the use of target cells with the same HLA haplotype as the host or a compatible HLA haplotype, said target cells being incubated with a synthetic peptide which sequence is a part of an HIV genome.

14. A process of stimulation in vivo of cytotoxic lymphocytes by exogenous antigen presentation without viral replication comprising: (A) administration of an HIV virus which infectious capacities have been inactivated or attenuated, but whose fusogenic capacities are intact according to claim 2; (B) optionally the cytotoxic T cells obtained after the step A above are tested in a cytotoxic test comprising: (i) the incubation of an organ or a biologic fluid of the host containing cytotoxic T cells of the host with a synthetic peptide which sequence is encoded by the viral genome contained partly in the first or the second plasmid; or (ii) the use of target cells with the same HLA haplotype as the host or a compatible HLA haplotype, said target cell being incubated with a synthetic peptide which sequence is a part of the sequence of an HIV genome.

15. A process of treatment of an eukaryotic host suffering from a viral pathology, wherein antigen presenting cells are treated with the immunogenic composition of claims 1 to 4 then administrated back to the mammal after incubation.

16. A process of screening a composition, which is capable of inducing against a viral pathology a cytotoxic response in vitro or in vivo by

endogenous antigen presentation without viral replication, wherein the cytotoxic activity of said composition is determined by the process according to claims 12 to 14.

17. A method of determining cytotoxic T lymphocyte (CTL) reponse to an antigen, wherein the method comprises: providing viral particles containing the antigen and having a fusogenic envelope membrane; targeting the viral particles into professional antigen presenting cells (APCs) by binding of the viral particles to the plasma membranes of the APCs and uptake of the viral particles by the APCs following fusion of the fusogenic envelope membranes of the viral particles with the plasma membranes of the APCs, which is followed by MHC-I-restricted presentation of the antigen by the APCs without viral replication or de novo, in situ synthesis of the antigen in the APCs; contacting the resulting transduced APCs with CTLs that recognize MHC-I-restricted antigen; and determining cell cytotoxicity resulting from said contact.

18. The method as claimed in claim 17, wherein the antigen is an HIV-1 antigen and the viral particles are attenuated or inactivated HIV-1 viral particles.

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=> file wpids
COST IN U.S. DOLLARS                              SINCE FILE     TOTAL
                                                       ENTRY   SESSION
FULL ESTIMATED COST                                     8.16      8.37

FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004
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MOST RECENT DERWENT UPDATE:       200427        <200427/DW>
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    NUMBERS. SEE ALSO:
    http://www.stn-international.de/archive/stnews/news0104.pdf <<<

>>> SINCE THE FILE HAD NOT BEEN UPDATED BETWEEN APRIL 12-16
    THERE WAS NO WEEKLY SDI RUN  <<<

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COST IN U.S. DOLLARS                               SINCE FILE     TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   3.78      12.15

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 29 Apr 2004 (20040429/PD)
FILE LAST UPDATED: 29 Apr 2004 (20040429/ED)
HIGHEST GRANTED PATENT NUMBER: US6728968
HIGHEST APPLICATION PUBLICATION NUMBER: US2004083524
CA INDEXING IS CURRENT THROUGH 29 Apr 2004 (20040429/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 29 Apr 2004 (20040429/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

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>>>  original, i.e., the earliest published granted patents or        <<<
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>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent             <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

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>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
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>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

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=> e buseyne florence/in
E1             3      BUSEY HUGH W/IN
E2             2      BUSEY PHILIP/IN
E3             1 --> BUSEYNE FLORENCE/IN
E4             3      BUSFIELD JOHN DAVID/IN
E5            16      BUSFIELD SAMANTHA J/IN
E6             1      BUSFIELD WALTER K/IN
E7             3      BUSGEN ALEXANDER/IN
E8             1      BUSGEN HERBERT/IN
E9             1      BUSH A MICHAEL/IN
E10            5      BUSH ADAM/IN
E11            8      BUSH ALAN M/IN
E12            1      BUSH ALBERT F/IN

=> s e3
L2             1 "BUSEYNE FLORENCE"/IN

=> s l2 not l1
L3             0 L2 NOT L1

=> e marsac delphine/in
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E2             1      MARSAC BERTRAND/IN
E3             1 --> MARSAC DELPHINE/IN
E4             1      MARSAC DIDIER/IN
E5             1      MARSAC JEAN YVES/IN
E6             1      MARSAC JEROME/IN
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E8            5     MARSACQ DIDIER/IN
E9            2     MARSAGLIA MICHAEL/IN
E10           1     MARSAGLIA MICHAEL C/IN
E11           6     MARSAI MARIA/IN
E12           5     MARSAIS CHRISTIAN/IN

=> s e3
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=> s l4 not l1
L5            0 L4 NOT L1

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E2            9     RIVIERE V ALFREDO/IN
E3            2 --> RIVIERE YVES/IN
E4            2     RIVIERRE BERNARD/IN
E5            2     RIVIERRE VALERIE/IN
E6            1     RIVIERS MARIE/IN
E7            1     RIVIEZZO ANTHONY L/IN
E8            1     RIVIEZZO FRED A/IN
E9            1     RIVIEZZO TONY L/IN
E10           1     RIVIEZZO VINCENT/IN
E11           1     RIVIEZZO VINCENT F/IN
E12           2     RIVILIS MIKHAIL EVSEEVICH/IN

=> s e3
L6            2 "RIVIERE YVES"/IN

=> s l6 not l1
L7            1 L6 NOT L1

=> d l7,ti,

L7   ANSWER 1 OF 1  USPATFULL on STN
TI     Moving picture film camera and film reel housing device


=> e heard jean michel/in
E1            7     HEARD JAMES L/IN
E2            1     HEARD JAMES T/IN
E3            6 --> HEARD JEAN MICHEL/IN
E4            1     HEARD JEFFERY GERALD/IN
E5            1     HEARD JIMMY/IN
E6            1     HEARD JIMMY C/IN
E7            1     HEARD JOHN P/IN
E8            1     HEARD JOSEPH MITCHELL/IN
E9            2     HEARD JR CHARLES B/IN
E10           1     HEARD JR CHARLES BEAN/IN
E11           1     HEARD JR RALPH L/IN
E12           2     HEARD JULIA/IN

=> s e3
L8            6 "HEARD JEAN MICHEL"/IN

=> s l8 not l1
L9            5 L8 NOT L1

=> d l9,ti,1-5

L9   ANSWER 1 OF 5  USPATFULL on STN
TI     Purified nucleic acid molecule for the expression of a lysosomal enzyme
       and use thereof for preventing or treating lysosomal storage diseases

L9   ANSWER 2 OF 5  USPATFULL on STN
```

TI Composition for the in vivo production of therapeutic products

L9 ANSWER 3 OF 5 USPATFULL on STN
TI Biocompatible implant for the expression and in vivo secretion of a therapeutic substance

L9 ANSWER 4 OF 5 USPATFULL on STN
TI Recombinant retroviral vector

L9 ANSWER 5 OF 5 USPATFULL on STN
TI Biocompatible implant for the expression and in vivo secretion of a therapeutic substance

=> d l9,cbib,ab,clm,1-5

L9 ANSWER 1 OF 5 USPATFULL on STN
2004:31080 Purified nucleic acid molecule for the expression of a lysosomal enzyme and use thereof for preventing or treating lysosomal storage diseases.
Desmaris, Nathalie, Roissey en Brie, FRANCE
Heard, Jean Michel, UNITED STATES
US 2004023218 A1 20040205
APPLICATION: US 2002-176066 A1 20020621 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A purified nucleic acid molecule which is capable of expressing a lysosomal enzyme wherein said nucleic acid molecule comprises at least a sequence coding for said lysosomal enzyme and a promoter highly active in the brain inserted upstream from said sequence.

CLM What is claimed is:

1. A purified nucleic acid molecule which is capable to express a lysosomal enzyme wherein said nucleic acid molecule comprises at least a sequence coding for said lysosomal enzyme and a promoter highly active in the brain inserted upstream from said sequence.

2. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule further comprises a posttranscriptional regulatory element inserted downstream from said sequence.

3. The nucleic acid molecule of claim 1, wherein the promoter highly active in the brain is the promoter of the phosphoglycerate kinase gene.

4. The nucleic acid molecule of claim 2, wherein the posttranscriptional regulatory element is a hepatitis virus posttranscriptional regulatory element.

5. The nucleic acid molecule of claim 1, wherein the sequence codes for an iduronidase (IDUA).

6. The nucleic acid molecule of claim 1, wherein the sequence codes for an arylsulphatase (ASA).

7. The nucleic acid molecule of claim 1, wherein the nucleic acid molecule further comprises at least one repeated AAV sequence involved in packaging and genome replication placed upstream from the promoter and/or downstream from the sequence coding for the lysosomal enzyme.

8. The nucleic acid molecule of claim 1, wherein the nucleic acid molecule further comprises at least one repeated AAV sequence involved in packaging and genome replication placed upstream from the promoter and/or downstream from the sequence coding for the posttranscriptional regulatory element.

9. A recombinant bacteria containing the nucleic acid molecule of claim 1, wherein said recombinant bacteria has been deposited at CNCM on Jun.

10. A recombinant bacteria containing the nucleic acid molecule of claim 1, wherein said recombinant bacteria has been deposited at CNCM on Jun. 20, 2002 under the reference I-2892.

11. A vector for the expression of a lysosomal enzyme, wherein said vector comprises the nucleic acid molecule of claim 1.

12. The vector of claim 11, wherein the vector is an adenovirus vector (AAV).

13. The vector of claim 11, wherein the vector is a lentivirus vector.

14. A cell transformed with the nucleic acid molecule of claim 1.

15. The cell of claim 14, wherein said cell is a mammal cell.

16. The cell of claim 14, wherein said cell is transformed ex vivo.

17. A method for preventing or treating a lysosomal storage disease in a mammal, wherein said method comprises administering the nucleic acid molecule of claim 1 to said mammalian host.

18. The method of claim 17, wherein said mammal is a human.

19. The method of claim 17, wherein said disease is MPS I or MPS IIIb.

20. A method for preventing or treating a lysosomal storage disease in a mammal, wherein said method comprises administering the vector of claim 11 to said mammalian host.

21. The method of claim 20, wherein said vector is administered by stereotactic method.

22. A method for preventing or treating a lysosomal storage disease in a mammal, wherein said method comprises the transfer of the cell of claim 14 into said mammalian host.

L9 ANSWER 2 OF 5 USPATFULL on STN

2002:268425 Composition for the in vivo production of therapeutic products.

Beuzard, Yves, Paris, FRANCE
Danos, Olivier, Garches, FRANCE
Descamps, Vincent, Marly le Roi, FRANCE
Heard, Jean-Michel, Paris, FRANCE
Moullier, Philippe, Meudon, FRANCE
Naffakh, Nadia, Malakoff, FRANCE
Perricaudet, Michel, Ecrosnes, FRANCE
Vainchenker, William, Paris, FRANCE
Aventis Pharma S.A., Antony, FRANCE (non-U.S. corporation)
US 6464998 B1 20021015
WO 9514785 19950601
APPLICATION: US 1996-649696 19960711 (8)
WO 1994-FR1359 19941122 19960711 PCT 371 date
PRIORITY: FR 1993-13977 19931123
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides cell compositions for in vivo implantation, and designed for the sustained and controlled delivery of therapeutic substances.

CLM What is claimed is:

1. A composition for transplantation in vivo comprising proliferating cells, a gelling agent, and a support to which said cell are anchored, wherein said cells comprise a replication defective recombinant adenovirus comprising at least one functional adenoviral gene and a

heterologous DNA sequence coding for a therapeutic product, whereby the heterologous DNA sequence is expressed and the product is produced.

2. The composition according to claim 1, wherein said cells are selected from the group consisting of fibroblasts, endothelial cells, epithelial cells, glial cells, hepatocytes, keratinocytes and myoblasts.

3. The composition according to claim 2, wherein said cells are fibroblasts.

4. The composition according to claim 1, wherein the cells are autologous with respect to an intended patient.

5. The composition according to claim 1, wherein the adenovirus is an adenovirus of human origin, canine origin, or an adenovirus comprising regions originating from a human adenovirus and a canine adenovirus.

6. The composition according to claim 5, wherein the adenovirus is selected from the group consisting of Ad2, Ad5 and CAV2.

7. The composition according to claim 1, wherein the therapeutic product is selected from the group consisting of peptides, polypeptides and proteins.

8. The composition according to claim 7, wherein the heterologous DNA sequence comprises signals enabling the therapeutic product to be produced and secreted.

9. The composition according to claim 7, wherein the therapeutic product is selected from the group consisting of enzymes, blood derivatives, insulin, variants of insulin, lymphokines, growth factors, apolipoproteins and antigenic polypeptides for the production of vaccines.

10. The composition according to claim 9, wherein said enzymes are selected from the group consisting of superoxide dismutase, catalase, amylases, lipases, amidases, and chymosin.

11. The composition according to claim 9, wherein said blood derivatives are selected from the group consisting of serum albumin, alpha-globin, beta-globin, factor VII, factor VIII, factor IX, von Willebrand factor, fibronectin and $\text{alpha}_{1\text{-antitrypsin}}$.

12. The composition according to claim 9, wherein said lymphokines are selected from the group consisting of the interleukins, interferons, colony stimulating factors, TNF, and TRF.

13. The composition according to claim 12, wherein said colony stimulating factors are selected from the group consisting of G-CSF, GM-CSF, M-CSF, and SCF.

14. The composition according to claim 9, wherein said growth factors are selected from the group consisting of growth hormone, erythropoietin, parathyroid hormone, FGF, EGF, PDGF, TGF, BNDF, NGF, and CNTF.

15. The composition according to claim 9, wherein said antigenic polypeptides are selected from the group consisting of antigens from hepatitis virus, cytomegalovirus, Epstein-Barr virus, and herpes virus.

16. The composition according to claim 1, wherein the gelling agent is selected from the group consisting of collagen, gelatin, glycosaminoglycans, fibronectin and lectins.

17. The composition according to claim 1, wherein the support is a solid, non-toxic and biocompatible support.

18. The composition according to claim 17, wherein the support is a biological support.

19. The composition according to claim 17, wherein the support is selected from the group consisting of crosslinked collagen, bone powder, carbohydrate-based polymers and limestone-based supports.

20. The composition according to claim 17, wherein the support is selected from polytetrafluoroethylene fibres.

21. A process for preparing the composition according to claim 1 comprising: a) removing a tissue sample from a body, b) isolating and culturing desired cells from said tissue sample, c) infecting the cultured cells with a replication defective recombinant adenovirus comprising at least one functional adenoviral gene and a heterologous DNA sequence coding for a therapeutic product, whereby the heterologous DNA sequence is expressed and the product is produced, d) incubating the infected cells with a medium containing a gelling agent thereby forming a mixture, e) depositing the mixture on a support, f) incubating the mixture under conditions permitting gelation of the gelling agent and anchorage of the cells to the support, and g) recovering the composition obtained in step (f).

22. The process according to claim 21, wherein the support in step e) is coated with the gelling agent.

23. The composition according to claim 1, comprising between 10^5 and 10^{10} cells.

24. The composition according to claim 1, comprising between 10^5 and 10^8 cells.

25. The composition according to claim 1, wherein the heterologous DNA sequence comprises a signal sequence.

L9 ANSWER 3 OF 5 USPATFULL on STN
2002:185315 Biocompatible implant for the expression and in vivo secretion of a therapeutic substance.
Moullier, Philippe, Meudon, FRANCE
Danos, Olivier, Garches, FRANCE
Heard, Jean-Michel, Paris, FRANCE
Ferry, Nicolas, Paris, FRANCE
INSTITUT PASTEUR, Paris, FRANCE, F-75724 (non-U.S. corporation)
US 2002098223 A1 20020725
APPLICATION: US 2001-987601 A1 20011115 (9)
PRIORITY: FR 1993-4700 19930421
FR 1993-9185 19930726
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to an implant obtained by assembling in vitro various elements in order to form a neo-organ which is introduced preferably in the peritoneal cavity of the recipient. The implant comprises a biocompatible support intended to the biological anchoring of cells; cells having the capacity of expressing and secreting naturally or after recombination a predetermined compound, for example a compound having a therapeutical interest; and a constituent capable of inducing and/or promoting the geling of said cells. The invention also relates to a kit for the preparation of the implant as well as to a new recombinant retroviral vector comprising a provirus DNA sequence modified in that the genes gag, pol and env have been deleted at least partially so as to obtain a proviral DNA capable of replication. The invention also relates to recombinant cells comprising the new retroviral vector.
CLM What is claimed is:

1. Implant characterized in that it comprises: a biocompatible support permitting the biological anchoring of cells, cells having the capacity to express and secrete naturally or after recombination a defined substance, for example a substance having therapeutic value; and a constituent capable of inducing and/or promoting the gelation of said cells.

2. Implant according to claim 1, characterized in that the biocompatible support includes at least me of the elements selected from the group comprising PTFE or a support of biological origin.

3. Implant according to claim 1, characterized in that the biocompatible support is a support of biological origin of the type resorbable in vivo at least partially.

4. Implant according to any one of the claims 1 to 3, characterized in that the biocompatible support is a calcium-based, in particular a calcium carbonate-based, support, preferably it is coral.

5. Implant according to claim 4, characterized in that the biocompatible support is high-porosity coral.

6. Implant according to claim 3 or claim 5, characterized in that the high-porosity coral is a spherical coral.

7. Implant according to any one of the claims 1 to 6, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is collagen, in particular type I collagen, preferably at a concentration of the order of 1.5 mg /ml.

8. Implant according to claim 1 or claim 3, characterized in that the biocompatible support is selected from: cross-linked collagen, in particular in the form of fibers or sponges, bone powder, carbohydrate-based polymers such as dextran or hyaluronic acid.

9. Implant according to any one of the claims 1 to 8, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is selected from supports based on: uncross-linked collagen, alginates.

10. Implant according to any one of the claims 1 to 9, characterized in that the cells are recombinant cells having the capacity to be tolerated immunologically by an organism to which they are administered, modified by a nucleotide sequence coding for a defined polypeptide.

11. Implant according to claim 10, characterized in that the recombinant cells are fibroblasts, in particular skin fibroblasts.

12. Implant according to any one of the claims 1 to 11, characterized in that said cells are recombinant cells modified by a retroviral vector comprising a proviral DNA sequence modified in a manner such that: the gag p and env genes of the proviral DNA have been deleted at least in part in order to produce a proviral DNA incapable of replicating this DNA being in addition incapable of recombining to form a wild-type virus, the LTR sequence contains a deletion in the sequence U3 such that transcription of the mRNA that it controls is reduced significantly for example at least 10-fold, and the recombinant retroviral vector comprises, in addition, an exogenous nucleotide sequence under the control of a promoter for example an exogenous, constitutive or inducible promoter.

13. Implant according to claim 12, characterized in that the proviral DNA of the vector is derived from the MuLV retrovirus.

14. Implant according to claim 11 or claim 12, characterized in that the sequences of the pol and env genes of the proviral DNA are entirely

deleted.

15. Implant according to any one of the claims 11 to 13, characterized in that the U3 region of the LTR3' fragment of the proviral DNA is deleted at the level of nucleotide 2797 of FIG. 1.

16. Implant according to any one of the claims 12 to 15, characterized in that the exogenous nucleotide sequence is under the control of the mouse PGK-1 promoter or the human PGK-1 promoter, optionally lacking a "TATA box".

17. Implant according to any one of the claims 12 to 16, characterized in that the proviral sequence upstream from the exogenous promoter is the proviral nucleotide sequence situated between nucleotides 1 and about 1500 of the sequence shorn in FIG. 1.

18. Implant according to any one of the claims 12 to 17, characterized in that the retroviral vector is the vector pM48 show in FIG. 2, modified by the insertion of the exogenous nucleotide sequence at the BamHI site.

19. Implant according to any one of the claims 1 to 10 or 12 to 18, characterized in that the recombinant cells are tumor cells.

20. Implant according to any one of the claims 1 to 19, characterized in that the recombinant cells are modified by a vector containing one or more exogenous nucleotide sequences coding for an antigen or an antigenic determinant or coding for a polypeptide or glycoprotein soluble in the serum, for example a polypeptide or a glycoprotein of therapeutic interest, in particular a hormone, a structural protein or glycoprotein or a metabolic protein or glycoprotein or a viral protein or glycoprotein or a protein having the characteristics of an antibody or an antibody fragment.

21. Implant according to any one of the claims 1 to 20, characterized in that it contains in addition one or more angiogenic factors, in particular bFGF.

22. Implant according to any one of the claims 1 to 21, characterized in that it contains heparin or a heparin derivative.

23. Implant according to any one of the claims 1 to 22, characterized in that it contains from 10^6 to 10^9, and preferably from 5×10^6 to 10^7 recombinant cells.

24. Use of an implant according to any one of the claims 1 to 23, in a permanent or temporary fashion, for the implantation in man or animals.

25. Use of an implant according to any one of the claims 1 to 23: either for the treatment of genetic diseases, in particular for the treatment of diseases of lysosomal overload, hemophilia A or hemophilia B, beta-thalassemia, the erogenous nucleotide sequence contained in the recombinant cells corresponding respectively to those which code for beta-glucuronidase, for the factor VIII factor IX or erythropoietin, or for an active part of these sequences; or for the treatment of acquired diseases, for example for the treatment of viral diseases in particular for the treatment of an infection due to the HIV retrovirus, for example by the expression and secretion into the serum of soluble CD4 molecules or a soluble anti-viral protein; or for the treatment of tumors, the exogenous nucleotide sequence contained in the recombinant cells coding for a substance capable of promoting or enhancing the immune response against the cells of the tumors.

26. Composition characterized in that it contains an implant according to any one of the claims 1 to 23 with one or more substances, in particular an antigen or an adjuvant.

27. Method of treatment of genetic diseases, acquired diseases or tumors, said method comprising the introduction into man or animals of an implant according to any one of the claims 1 to 23 for a period of time sufficiently long to allow the cells included in said implant to produce in vivo a peptide, a protein or a glycoprotein having a therapeutic effect on the disease to be treated.

28. Method according to claim 7, characterized in that said implant is introduced in the peritoneal cavity, the peri-renal space or the skin of the patient to be treated.

29. Method of preparation of an implant according to any one of the claims 1 to 23, said method comprising the steps of: placing of the biocompatible support in contact with said cells and a constituent capable of inducing and/or promoting their gelation; incubation of the preparation obtained in the previous step in order to obtain the gelation of said constituents; culture of the cells thus obtained under conditions allowing them to bind to the gelled constituents, and recovery of the implant thus obtained.

30. Method according to claim 29, characterized in that the biocompatible support is placed in contact with cells previously incorporated into a solution of collagen.

31. Method according to claim 29 or 30, characterized in that the biocompatible support is constituted of PTFE fibers or coral powder, previously treated with a solution of collagen or a growth factor.

32. Recombinant retroviral vector characterized in that it comprises: a proviral DNA sequence modified in a manner such that: the gag, pol and env genes of the proviral DNA have been deleted at least in part in order to produce a proviral DNA incapable of replication, this DNA being in addition unable to recombine for form a wild-type virus, the LTR sequence bears a deletion in the U3 sequence such that transcription of mRNA that it controls is reduced significantly, for sample by at least 10 fold, and the recombinant retroviral vector comprising in addition an exogenous nucleotide sequence under the control of a promoter for example an exogenous, inducible or constitutive promoter.

33. Retroviral vector according to claim 32, characterized in that the modified proviral DNA sequence, the exogenous nucleotide sequence and the exogenous promoter are borne by a plasmid.

34. Retroviral vector according to claim 1 or claim 33, characterized in that the proviral DNA is derived from the MuLV retrovirus.

35. Retroviral vector according to any one at the claims 32 to 34, characterized in that the sequences for the pol and env genes of the proviral DNA are entirely deleted.

36. Retroviral vector according to any one of the claims 32 to 35, characterized in that the U3 region of the LTR3' fragment is deleted at the level of nucleotide 2797 of FIG. 1.

37. Retroviral vector according to any one of the claims 32 to 36, characterized in that the exogenous nucleotide sequence is under the control of the mouse PGK-1 promoter or the human PGK-1 promoter, optionally lacking a "TATA box".

38. Retroviral vector according to any one of the claims 32 to 36, characterized in that the proviral sequence upstream from the exogenous promoter is the proviral nucleotide sequence situated between the nucleotides 1 and about 1500 of the sequence shown in FIG. 1.

39. Retroviral vector according to claim 37, characterized in that the

exogenous nucleotide sequence is inserted at the BamHI site downstream from the exogenous constitutive PGK-1 promoter.

40. Retroviral vector according to any one of the claims 32 and 39, characterized in that it is the pM48 vector shown in FIG. 2, modified by the insertion of the exogenous nucleotide sequence at the BamHI site.

41. Retroviral vector according to any one of the claims 32 to 40, characterized in that it contains at the BamHI site downstream from the exogenous constitutive promoter a BamHI fragment of the gene of beta-galactosidase.

42. Retroviral vector acceding to any one of the claim 32 to 41, characterized in that it contains in addition upstream from the exogenous constitutive promoter an enhancer sequence.

43. Recombinant cells characterized in that they are cells having the capacity to be tolerated immunologically by the organism to which they are administered, modified by a retroviral vector according to any one of the claims 32 to 42.

44. Recombinant cells according to claim 43, characterized in that they are recombinant fibroblasts, in particular skin fibroblasts.

45. Recombinant cells according to claim 43, characterized in that they are tumor cells modified by a retroviral vector according to any one of the claims 32 to 42.

46. Recombinant cells according to any one of the claims 43 to 45, characterized in that the exogenous nucleotide sequence which they contain codes for a protein whose expression is desired, in particular a protein soluble in the serum.

47. Recombinant cells according to any one of the claims 43 to 46, characterized in that the exogenous nucleotide sequence which they contain codes for beta-glucuronidase.

48. Use of the recombinant cells according to any one of the claims 43 to 47 for the treatment of a disease capable of being corrected by the expression and secretion into the serum of a patient of the exogenous nucleotide sequence contained in these cells.

49. Use of the recombinant cells according to any one of the claims 43 to 47 for the treatment of genetic diseases, in particular for the treatment of diseases of lysosomal overload, hemophilia A or hemophilia B, beta-thalassemia, the exogenous nucleotide sequence contained in the recombinant cells corresponding respectively to those which code for beta-glucuronidase for the factor VIII, factor IX or erythropoietin or for an active part of these sequences.

50. Use of the recombinant cells according to any one of the claims 43 to 47 for the treatment of acquired diseases, for Ocala for the treatment of viral diseases, in particular for the treatment of an infection due to the HIV retrovirus for example by the expression and secretion into the serum of soluble CD4 molecules or of a soluble anti-viral protein.

51. Use of the recombinant cells according to any one of the claims 43 to 47 for the preparation of antibodies against the expression product of the exogenous nucleotide sequence contained in the recombinant cells.

52. Use of the recombinant cells according to any one o the claims 43 to 47 for the treatment of tumors, the exogenous nucleotide sequence contained in the recombinant cells coding for a substance capable of promoting or enhancing the immune response against the cells of the tumor.

53. Recombinant cells according to claim 52 such as obtained by recombination of tumor cells with a retroviral vector according to any one of the claims 32 to 42.

54. Kit for the preparation of an implant to achieve the in vivo expression and secretion by cells of a substance to produce a desired therapeutic effect, said kit containing: a biocompatible support making possible the biological anchoring of said cells; and a constituent capable of inducing and/or promoting the gelation of said cells.

55. Kit according to claim 54, characterized in that the biocompatible support comprises at least one of the elements selected from the group including PTFE or a support of biological origin, in particular a calcium-based, in particular a calcium carbonate-based, support of biological origin, preferably coral.

56. Kit according to claim 54 or 55, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is collagen, in particular type I collagen, preferably at a concentration of the order of 1.5 mg/ml.

57. Kit according to claim 54, characterized in that it contains a DNA comprising a sequence coding for the substance expressed and secreted by said cells.

58. Kit according to claim 57, characterized in that it contains a retroviral vector according to any one of the claims 32 to 42.

59. Kit according to any one of the claims 54 to 58, characterized in that it contains cells having the capacity to express and secrete naturally CT after recombination a defined substance for example a substance having a therapeutic value.

60. Kit according to claim 59, characterized in that the cells are recombinant cells a according to anyone of the claims 43 to 47.

L9 ANSWER 4 OF 5 USPATFULL on STN
2001:220880 Recombinant retroviral vector.
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Danos, Olivier, Garches, France
Heard, Jean-Michel, Paris, France
Ferry, Nicolas, Paris, France
Institut Pasteur, Paris, France (non-U.S. corporation)
US 6326195 B1 20011204
APPLICATION: US 1999-225509 19990106 (9)
PRIORITY: FR 1993-4700 19930421
FR 1993-9185 19930726
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to an implant obtained by assembling in vitro various elements in order to form a neo-organ which is introduced preferably in the peritoneal cavity of the recipient. The implant comprises a biocompatible support intended to the biological anchoring of cells; cells having the capacity of expressing and secreting naturally or after recombination a predetermined compound, for example a compound having a therapeutical interest; and a constituent capable of inducing and/or promoting the geling of said cells. The invention also relates to a kit for the preparation of the implant as well as to a new recombinant retroviral vector comprising a provirus DNA sequence modified in that the genes gag, pol and env have been deleted at least partially so as to obtain a proviral DNA capable of replication. The invention also relates to recombinant cells comprising the new retroviral vector.
CLM What is claimed is:

1. A recombinant retroviral vector comprising: a proviral DNA sequence upstream of an exogenous nucleotide sequences, wherein the proviral DNA sequence is the nucleotide sequence situated between nucleotides 1 and about 1500 SEQ ID NO:1, in order to produce a proviral DNA incapable of replication, this DNA being in addition unable to recombine to form a wild-type virus, wherein the LTR of said proviral DNA sequence bears a deletion in the U3 sequence that reduces the transcription of mRNA that it controls at least ten-fold; and an exogenous nucleotide sequence under the control of a promoter.

2. The retroviral vector according to claim 1, wherein said modified proviral DNA sequence, the exogenous nucleotide sequence and the promoter are inserted in a plasmid.

3. The retroviral vector according to claim 1, wherein said proviral DNA is derived from a MuLV retrovirus.

4. The retroviral vector according to claim 1, wherein the sequences for the pol and env genes of the proviral DNA are entirely deleted.

5. The retroviral vector according to claim 1, wherein the U3 region of the LTR3' fragment is deleted at nucleotide position 2797 of SEQ ID NO;1.

6. The retroviral vector according to claim 1, wherein said exogenous nucleotide sequence is under the control of a mouse PGK-1 promoter or a human PGK-1 promoter, optionally lacking a "TATA box".

7. The retroviral vector according to claim 6, wherein said nucleotide sequence is inserted at a BamHI site downstream from the PGK-1 promoter.

8. The retroviral vector according to claim 1, comprising the pM48 vector shown in FIG. 2, wherein the exogenous nucleotide sequence is inserted at the BamHI site.

9. The retroviral vector according to claim 1, comprising at a BamHI site downstream from the promoter a BamHI fragment of a lacZ gene.

10. The retroviral vector according to claim 1, further comprising upstream from the promoter an enhancer sequence.

11. Transduced cells being tolerated immunologically by the organism to which they are administered, comprising the retroviral vector according to claim 1.

12. The transduced cells according to claim 11, wherein the cells are fibroblasts.

13. The transduced cells according to claim 11, wherein the cells are tumor cells.

14. The transduced cells according to claim 11, wherein the exogenous nucleotide sequence codes for a protein whose expression is desired.

15. The transduced cells according to claim 11, wherein the exogenous nucleotide sequence codes for beta-glucuronidase.

16. Isolated transduced cells obtained by transducing tumor cells with the retroviral vector according to claim 1.

L9 ANSWER 5 OF 5 USPATFULL on STN
1999:61004 Biocompatible implant for the expression and in vivo secretion of a therapeutic substance.
Moullier, Philippe, Meudon, France
Danos, Olivier, Garches, France

Ferry, Nicolas, Paris, France
Institut Pasteur, Paris Cedex, France (non-U.S. corporation)
US 5906817 19990525
WO 9424298 19941027
APPLICATION: US 1996-532814 19960119 (8)
WO 1994-FR456 19940421 19960119 PCT 371 date 19960119 PCT 102(e) date
PRIORITY: FR 1993-4700 19930421
FR 1993-9185 19930726
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to an implant obtained by assembling in vitro various elements in order to form a neo-organ which is introduced preferably in the peritoneal cavity of the recipient. The implant comprises a biocompatible support intended to the biological anchoring of cells; cells having the capacity of expressing and secreting naturally or after recombination a predetermined compound, for example a compound having a therapeutical interest; and a constituent capable of inducing and/or promoting the gelling of said cells. The invention also relates to a kit for the preparation of the implant as well as to a new recombinant retroviral vector comprising a provirus DNA sequence modified in that the genes gag, pol and env have been deleted at least partially so as to obtain a proviral DNA capable of replication. The invention also relates to recombinant cells comprising the new retroviral vector.

CLM What is claimed is:

1. An implant comprising: (a) a biocompatible support permitting the biological anchoring of cells, wherein said biocompatible support comprises high porosity coral; (b) cells transduced by a nucleotide sequence encoding a defined polypeptide and having the capacity to express said polypeptide; and (c) a constituent capable of inducing and/or promoting the gelation of said cells.

2. The implant according to claim 1, wherein said biocompatible support is at least partially resorbable in vivo.

3. The implant according to claim 1, wherein said high-porosity coral biocompatible support has a spherical shape.

4. The implant according to claim 1, wherein said constituent capable of inducing and/or promoting the gelation of the cells is collagen.

5. The implant according to claim 1, wherein said constituent capable of inducing and/or promoting the gelation of the cells is selected from supports based on: uncross-linked collagen, or alginates.

6. The implant according to claim 1, wherein said cells have the capacity to be tolerated immunologically by an organism to which they are administered, and have been transduced by a nucleotide sequence coding for a defined polypeptide.

7. The implant according to claim 6, wherein said transduced cells are fibroblasts.

8. The implant according to claim 1, wherein said transduced cells comprise a retroviral vector comprising a proviral DNA sequence in which: the gag, pol and env genes of the proviral DNA have been deleted at least in part in order to produce a proviral DNA incapable of replicating this DNA being in addition incapable of recombining to form a wild-type virus, the LTR sequence contains a deletion in the sequence U3 such that transcription of the mRNA that it controls is reduced, and the retroviral vector comprises, in addition, an exogenous nucleotide sequence under the control of a promoter.

9. The implant according to claim 8, wherein said proviral DNA of the vector is derived from the MuLV retrovirus.

10. The implant according to claim 8, wherein said sequences of the pol and env genes of the proviral DNA are entirely deleted.

11. The implant according to claim 8, wherein the U3 region of the LTR3' fragment of the proviral DNA is deleted at nucleotide 2797 of SEQ ID NO:1.

12. The implant according to claim 8, wherein said exogenous nucleotide sequence is under the control of the mouse PGK-1 promoter or the human PGK-1 promoter, optionally lacking a "TATA box".

13. The implant according to claim 8, wherein said proviral sequence upstream from a promoter of the exogenous nucleotide sequence is the proviral nucleotide sequence situated between nucleotides 1 and about 1500 of SEQ ID NO:1.

14. The implant according to claim 8, wherein said retroviral vector is the vector pM48 shown in FIG. 2, comprising the exogenous nucleotide sequence at the BamHI site.

15. The implant according to claim 1, wherein said cells are tumor cells transduced with an exogenous nucleotide sequence.

16. The implant according to claim 1, wherein said cells are transduced with a vector containing one or more exogenous nucleotide sequences coding for an antigen or an antigenic determinant or coding for a polypeptide or glycoprotein soluble in the serum.

17. The implant according to claim 1, further comprising one or more angiogenic factor.

18. The implant according to claim 1, further comprising heparin or a heparin derivative.

19. The implant according to claim 1, comprising from 10^6 to 10^9 transduced cells.

20. A method of temporary or permanent delivery of a desired polypeptide to a human or animal comprising implanting into the human or animal an implant according to claim 1.

21. A method for administering cells to a human or animal comprising implanting into the human or animal an implant according to claim 1: either for the treatment of genetic diseases, wherein an exogenous nucleotide sequence contained in the cells code for beta-glucuronidase, for the factor VIII, factor IX or erythropoietin; or for the treatment of acquired diseases; or for the treatment of tumors, wherein the exogenous nucleotide sequence contained in the transduced cells code for a substance capable of promoting or enhancing the immune response against the cells of the tumors.

22. A composition comprising an implant according to claim 1 with one or more substances.

23. A method of treatment of genetic diseases, acquired diseases or tumors, said method comprising the introduction into man or animals of an implant according to claim 1 for a period of time sufficiently long to allow the cells included in said implant to produce in vivo a peptide, a protein or a glycoprotein having a therapeutic effect on the disease to be treated.

24. A method according to claim 23, wherein said implant is introduced in the peritoneal cavity, the peri-renal space or the skin of the patient to be treated.

25. A method of preparation of an implant according to claim 1, said method comprising the steps of: placing of the biocompatible support in contact with said cells and a constituent capable of inducing and/or promoting their gelation; incubation of the preparation obtained in the previous step in order to obtain the gelation of said constituents; culture of the cells thus obtained under conditions allowing them to bind to the gelled constituents and recovery of the implant thus obtained.

26. The method according to claim 25, wherein said biocompatible support is placed in contact with cells previously incorporated into a solution of collagen.

27. The method according to claim 25, wherein said biocompatible support is constituted of coral powder, previously treated with a solution of collagen or a growth factor.

28. A kit for the preparation of an implant to achieve the in vivo expression and secretion by cells of a substance to produce a desired therapeutic effect, said kit containing: a biocompatible support comprising high porosity coral making possible the biological anchoring of said cells; and a constituent capable of inducing and/or promoting the gelation of said cells.

29. The kit according to claim 28, wherein said constituent capable of inducing and/or promoting the gelation of the cells is collagen.

30. The kit according to claim 28 comprising a DNA comprising a sequence coding for the substance expressed and secreted by said cells.

31. A kit for the preparation of an implant to achieve the in vivo expression and secretion by cells of a substance to produce a desired therapeutic effect, said kit containing: a biocompatible support comprising high porosity coral making possible the biological anchoring of said cells; a constituent capable of inducing and/or promoting the gelation of said cells; and the retroviral vector according to claim 8.

32. The kit according to claim 28, comprising cells having the capacity to express and secrete naturally or after recombination a defined substance.

33. A kit for the preparation of an implant to achieve the in vivo expression and secretion by cells of a substance to produce a desired therapeutic effect, said kit containing: a biocompatible support comprising high porosity coral making possible the biological anchoring of said cells; and a constituent capable of inducing and/or promoting the gelation of said cells wherein said cells are transduced cells having the capacity to be tolerated immunologically by the organism to which they are administered, and wherein said cells comprise a retroviral vector according to claim 8.

34. An implant comprising: (a) a biocompatible support permitting the biological anchoring of cells, wherein said support consists of high-porosity coral, (b) fibroblast cells transduced by a nucleotide sequence encoding a polypeptide and having the capacity to express and secrete said polypeptide; and (c) a constituent capable of inducing and/or promoting the gelation of said cells, wherein said constituent is collagen.

35. An implant comprising: (a) a biocompatible support permitting the biological anchoring of cells, wherein said support consists of high-porosity coral, (b) cells transduced by a retroviral vector comprising a nucleotide sequence encoding a polypeptide and having the capacity to express and secrete said polypeptide; and (c) a constituent capable of inducing and/or promoting the gelation of said cells, wherein said constituent is collagen.

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E6           33      SCHWARTZ P/IN
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E12           1      SCHWARTZ P L/IN

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            14 "SCHWARTZ O"/IN
             1 "SCHWARTZ O H"/IN
             1 "SCHWARTZ O N"/IN
L10         16 ("SCHWARTZ O"/IN OR "SCHWARTZ O H"/IN OR "SCHWARTZ O N"/IN)

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L10  ANSWER 1 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Shutter comprises flexible edges moving in guide tracks into which they
     are reinserted by guide members opposite tracks when shutter moves
     upwards.

L10  ANSWER 2 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Dust absorption robot is controlled by sensors which reverse it on contact
     and potentiometer which measures resistance corresponding to largest part
     distance which robot covers.

L10  ANSWER 3 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New immunogenic composition capable of inducing a cytotoxic response
     through MHC-1 restricted exogenous antigen presentation pathway, useful
     for the treatment of viral pathologies, such as those due to HIV-1 or
     HIV-2 infections.

L10  ANSWER 4 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Mouthpiece for vacuum cleaner - works with machine having combination of
     rotating and static brush rollers instead of combined flat mouthpiece or
     brush mouthpiece, on soft or hard floor.

L10  ANSWER 5 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Bladed unit such as snowplough, road plane or similar - has frame
     supporting blade and mounted on vehicle, blade being divided into several
     parts or modules.

L10  ANSWER 6 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New O-glycosyl-pyrimidine nucleoside derivs. - with anti-retroviral
     activity, esp. for treatment of AIDS.

L10  ANSWER 7 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Charging and unloading device for circuit board processor - has
     cooperating gripper elements between storage magazine and transport
     conveyor.

L10  ANSWER 8 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Charging device for circuit board component mounting machine - has
     vertically and horizontally displaced gripper transferring circuit boards
     between ready position and loading position.

L10  ANSWER 9 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Magazine for steps or flat building components - has separate safety lock
     for each receiving level.

L10  ANSWER 10 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Double function vacuum cleaner - has mouthpiece with dust container
     connectable to hose when fan unit used for cleaning items above floor
     level.

L10  ANSWER 11 OF 16  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Picture tracking and colouring board - comprises transparent board
```

supporting transparent sheet with picture and second reflective board.

L10 ANSWER 12 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Vacuum cleaner suction nozzle assembly - has narrow intake slit for air with tilting brushes on either side of it.

L10 ANSWER 13 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Height adjuster for vacuum cleaner - locks operating shaft relative to lower casing.

L10 ANSWER 14 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Vacuum cleaner dust collector bag - has hose attachment and sealing device consisting of slotted elastic membrane fitting over hole in bag.

L10 ANSWER 15 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Electrically operated vacuum cleaner - has adjustable throttle in suction tube with finger operated sliding button and electronic motor control.

L10 ANSWER 16 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
TI Coaxial cable connector system - has conducting hollow cone forced between cable inner insulation and outer conductor.

=> d l10,bib,ab,3

L10 ANSWER 3 OF 16 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2002-713486 [77] WPIDS
DNN N2002-562862 DNC C2002-202320
TI New immunogenic composition capable of inducing a cytotoxic response through MHC-1 restricted exogenous antigen presentation pathway, useful for the treatment of viral pathologies, such as those due to HIV-1 or HIV-2 infections.
DC B04 D16 S03
IN BUSEYNE, F; HEARD, J; MARSAC, D; MICHEL, M; RIVIERE, Y; **SCHWARTZ, O**
PA (CNRS) CNRS CENT NAT RECH SCI; (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (INSP) INST PASTEUR; (BUSE-I) BUSEYNE F; (HEAR-I) HEARD J; (MARS-I) MARSAC D; (MICH-I) MICHEL M; (RIVI-I) RIVIERE Y; (SCHW-I) SCHWARTZ O; (CNRS) CENT NAT RECH SCI
CYC 101
PI WO 2002072140 A2 20020919 (200277)* EN 96
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2002172683 A1 20021121 (200279)
EP 1363662 A2 20031126 (200380) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002072140 A2 WO 2002-EP2620 20020226; US 2002172683 A1 Provisional US 2001-271432P 20010227, US 2002-83678 20020227; EP 1363662 A2 EP 2002-708352 20020226, WO 2002-EP2620 20020226
FDT EP 1363662 A2 Based on WO 2002072140
PRAI US 2001-271432P 20010227; US 2002-83678 20020227
AB WO 200272140 A UPAB: 20021129
NOVELTY - An immunogenic composition (I) capable of inducing a cytotoxic response in vitro or in vivo against a viral disease through a major histocompatibility complex class I (MHC-1) restricted exogenous antigen presentation pathway without requiring viral replication, is new.
DETAILED DESCRIPTION - An immunogenic composition (I) comprises at least one of the following compounds:
(a) a plasmid containing a polynucleotide corresponding to the entire or a part of the viral genome and a second plasmid comprising an insert

containing a polynucleotide coding for a viral envelope and being under the control of a promoter, the plasmids being selected for their fusogenic properties when binding to antigen presentation cells, and for inducing a cytotoxic response through a MHC-1 restricted exogenous antigen presentation pathway;

(b) a plasmid comprising a polynucleotide coding for the entire or a part of the virus genome and contains an insert containing a polynucleotide coding for a viral envelope, and being under the control of a promoter, the plasmids being selected for their fusogenic non-replicative properties when binding to antigen presentation cells, and for inducing a cytotoxic response through a CMH-2 restricted exogenous antigen presentation pathway;

(c) a virus with intact fusogenic capacities, but whose infectious capacities have been inactivated or attenuated; and

(d) viral particles obtained by the purification of a cell culture supernatant.

INDEPENDENT CLAIMS are also included for the following:

(1) a vaccinating composition containing (I) with a carrier or another vaccine, and obtained by the process of (2);

(2) screening a composition which is capable of inducing against a viral pathology a cytotoxic response in vitro or in vivo by exogenous antigen presentation without viral replication, where the cytotoxic activity of the composition is determined by the process of (6);

(3) a process of treatment of a eukaryotic host suffering from a viral pathology comprising administering a plasmid comprising a polynucleotide coding for the entire or a part of the virus genome and containing an insert containing a polynucleotide coding for a viral envelope, or coadministering a first plasmid comprising the entire or a part of the virus genome and a second plasmid comprising an insert containing a polynucleotide coding for a viral envelope, and being under the control of a promoter, the plasmids being selected for their fusogenic properties when binding to antigen presentation cells, and for inducing a cytotoxic response through a MHC-1 or CMH-1 restricted exogenous antigen presentation pathway;

(4) a process of stimulation in vivo of cytotoxic lymphocytes through an MHC-1 restricted exogenous antigen presentation pathway without requiring viral replication;

(5) a process of treatment of an eukaryotic host suffering from a viral pathology, where antigen presenting cells are treated with (I) then administered back to the mammal after incubation; and

(6) determining cytotoxic T lymphocyte (CTL) response to an antigen.

ACTIVITY - Virucide; Anti-HIV (human immunodeficiency virus).

MECHANISM OF ACTION - Gene therapy; MHC-Binding-Inhibitor-I; Vaccine.

A study was made on female H-2 BALB/c mice 6-8 weeks old to determine whether co-injection of a VSV expression plasmid in the presence of a Gag expression vector would enable the in vivo anti-Gag cytotoxic response to increase. When the combination 75 micro g pR8.2 + 25 micro g pCMV-AS was injected, the appearance of anti-Gag CTL was observed in 2 mice out of 3 at 2 weeks post injection. In the presence of the VSV vector, the effectiveness seemed better since 3 mice out of 3 responded.

USE - The methods and compositions of the present invention are useful for the treatment of viral pathologies, such as those due to human immunodeficiency virus (HIV)-1 or HIV-2 infections.

Dwg.0/9

```
=> buseyne f/in
BUSEYNE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> e buseyne f/in
E1             2      BUSEY H W/IN
E2             1      BUSEY J W/IN
E3             1 --> BUSEYNE F/IN
```

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E5            1      BUSFIELD J/IN
E6            4      BUSFIELD J D/IN
E7            1      BUSFIELD S/IN
E8           20      BUSFIELD S J/IN
E9            1      BUSFIELD W K/IN
E10           1      BUSFY L/IN
E11           3      BUSGEN A/IN
E12           1      BUSGEN H/IN

=> s e3
L11           1 "BUSEYNE F"/IN

=> s l11 not l10
L12           0 L11 NOT L10

=> e marsac d/in
E1            1      MARSAASHV G P/IN
E2            1      MARSAC B/IN
E3            2 --> MARSAC D/IN
E4            3      MARSAC J/IN
E5            4      MARSAC J Y/IN
E6            1      MARSAC N T/IN
E7            2      MARSAC Y/IN
E8           16      MARSACQ D/IN
E9            1      MARSAGISHV G P/IN
E10           1      MARSAGISHV M A/IN
E11           2      MARSAGISHV T S A/IN
E12           1      MARSAGISHVILI G P/IN

=> s e3
L13           2 "MARSAC D"/IN

=> s l13 not l10
L14           1 L13 NOT L10

=> d l14,ti,

L14   ANSWER 1 OF 1  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI    Mfr. of highly dielectric material strength for power transmission cable
      insulation - involves impregnating insulating granules with dissolved
      conducting material before evaporation and drying of solvent to produce
      required dielectric.


=> e riviere y/in
E1           10      RIVIERE V A/IN
E2            1      RIVIERE W L/IN
E3            7 --> RIVIERE Y/IN
E4            1      RIVIERE Y A/IN
E5            1      RIVIEREAUDEBERT J/IN
E6            1      RIVIERELLO M/IN
E7            2      RIVIERRE B/IN
E8            3      RIVIERRE D/IN
E9            3      RIVIERRE V/IN
E10           2      RIVIERRE VIER V/IN
E11           1      RIVIEZZO A L/IN
E12           1      RIVIEZZO D/IN

=> s e3 or e4
              7 "RIVIERE Y"/IN
              1 "RIVIERE Y A"/IN
L15           7 "RIVIERE Y"/IN OR "RIVIERE Y A"/IN

=> s l15 not l10
L16           6 L15 NOT L10
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```
=> d l16,ti,1-6

L16  ANSWER 1 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Movie film reel has film end locked in hub slit by flange projections.

L16  ANSWER 2 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Cine camera film reel receiver - has receiving plate for reels with space
     for film guides and rear pressure plate.

L16  ANSWER 3 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Cassette for photosensitive product, esp cinematographic films - has core
     on which photographic product is wound before exposure and core designed
     to receive product after exposure.

L16  ANSWER 4 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New immunogenic peptide(s) derived from envelope glyco protein(s) of HIV-1
     - for diagnosing and preventing HIV-1 infection.

L16  ANSWER 5 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Continuous developer for photographic film - has multiple development
     tanks, each containing film feed rollers.

L16  ANSWER 6 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   Frame positioner for camera - has integral film advance rollers adjacent
     gap between exposure apertures.


=> d l16,bib,ab,4

L16  ANSWER 4 OF 6  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   1993-047142 [06]   WPIDS
DNC  C1993-021201
TI   New immunogenic peptide(s) derived from envelope glyco protein(s) of HIV-1
     - for diagnosing and preventing HIV-1 infection.
DC   B04 D16
IN   BARRE-SINOUSSI, F; DARTEVELLE, S; DEMERET, C; MAZIE, J C; RIVIERE, Y;
     TRAINCARD, F
PA   (INSP) INST PASTEUR
CYC  1
PI   FR 2677364      A1 19921211 (199306)*      34
ADT  FR 2677364 A1 FR 1991-6826 19910605
PRAI FR 1991-6826         19910605
AB   FR   2677364 A UPAB: 19931119
     New immunogenic peptide sequences (I) correspond to all or part of the
     chain VVIRSANFTDNAKT, opt. modified by substitution, deletion or addn. of
     at least one amino acid.
          Also new are (1) hybrid molecules (II) contg. (I) plus a heterologous
     amino acid chain or particle able to generate antibodies specific for (I);
     (2) oligomers (Ia) contg. at least 2 (I) units; (3) nucleic acid (III)
     which encodes (I); (4) polyclonal and monoclonal antibodies (Ab) able to
     recognise (I) and (5) hybridomas which produce monoclonal Ab.
          Specifically, (I) contain as a min. the sequence NFTDN and (II)
     contain as their heterologous component bovine serum albumin; hepatitis B
     surface antigen; lam B; malE or keyhole limpet haemocyanin.
          USE - (I), or equivalently (II) and (Ia), induce formation of
     antibodies which neutralise HIV (specifically the HIV-1 isolates BRU, MN
     and RF) so are useful in protective vaccines, opt. together with other
     immunogenic HIV sequences. Ab can be used to diagnose presence of
     HIV-antigens while (I) can be used to detect HIV-related antibodies and
     for treatment of HIV infections. Anti-idiotypic antibodies, raised against
     Ab, can be used to detect antibodies, as immunogens and in immunotherapy.
     Viruses or bacteria transformed with (III) may be used as live vaccines.
     Dwg.0/0
```

```
=> e heard j/in
E1           2     HEARD H/IN
E2           1     HEARD H L/IN
E3          27 --> HEARD J/IN
E4           1     HEARD J C/IN
E5           5     HEARD J E/IN
E6           2     HEARD J G/IN
E7           1     HEARD J L/IN
E8           2     HEARD J M/IN
E9           1     HEARD J S/IN
E10          1     HEARD J T/IN
E11          1     HEARD K A/IN
E12          1     HEARD K C/IN

=> s e8
L17          2 "HEARD J M"/IN

=> s l17 not l10
L18          2 L17 NOT L10

=> d l18,ti,1-2

L18  ANSWER 1 OF 2  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   New purified nucleic acid molecules capable of expressing a lysosomal
     enzyme, useful for preventing or treating lysosomal storage diseases (e.g.
     Gaucher type I disease or Sanfilippo disease) in humans.

L18  ANSWER 2 OF 2  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
TI   An untwisting frame for cable yarns - has yarn attachment arm pairs
     radially secured to a rotatable connector leg.


=> d l18,bib,ab

L18  ANSWER 1 OF 2  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2004-142648 [14]   WPIDS
DNC  C2004-057257
TI   New purified nucleic acid molecules capable of expressing a lysosomal
     enzyme, useful for preventing or treating lysosomal storage diseases (e.g.
     Gaucher type I disease or Sanfilippo disease) in humans.
DC   B04 D16
IN   DESMARIS, N; HEARD, J M
PA   (DESM-I) DESMARIS N; (HEAR-I) HEARD J M
CYC  1
PI   US 2004023218   A1 20040205 (200414)*      20
ADT  US 2004023218 A1 US 2002-176066 20020621
PRAI US 2002-176066         20020621
AB   US2004023218 A UPAB: 20040226
     NOVELTY - A purified nucleic acid molecule capable of expressing a
     lysosomal enzyme, is new. The nucleic acid molecule comprises at least a
     sequence coding for the lysosomal enzyme and a promoter highly active in
     the brain inserted upstream from the sequence.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
     following:
          (1) a recombinant bacteria containing the above nucleic acid
     molecule, where the recombinant bacteria has been deposited at CNCM on
     June 20, 2002 under the reference I-2891 or I-2892;
          (2) a vector for the expression of a lysosomal enzyme, the vector
     comprising the nucleic acid molecule cited above;
          (3) a cell transformed with the new nucleic acid molecule; and
          (4) methods for preventing or treating a lysosomal storage disease in
     a mammal, comprising administering the above nucleic acid molecule or
     vector to the mammalian host, or transferring the cell cited above into
     the mammalian host.
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        MECHANISM OF ACTION - Gene therapy.
        USE - The composition and methods are useful for preventing or
     treating lysosomal storage diseases (e.g. Gaucher type I disease, Hurler
     disease or Sanfilippo disease) in humans.
     Dwg.0/4


=> file medline
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        47.97      79.32

FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004

 FILE LAST UPDATED: 28 APR 2004 (20040428/UP).  FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e schwartz o/au
E1             2      SCHWARTZ NATHAN H/AU
E2             1      SCHWARTZ NELSON D/AU
E3            90 --> SCHWARTZ O/AU
E4             2      SCHWARTZ O A/AU
E5             3      SCHWARTZ O D/AU
E6             5      SCHWARTZ O M/AU
E7            10      SCHWARTZ OLIVIER/AU
E8             1      SCHWARTZ OWEN/AU
E9             1      SCHWARTZ OWEN M/AU
E10          219      SCHWARTZ P/AU
E11           17      SCHWARTZ P A/AU
E12          204      SCHWARTZ P E/AU

=> s e7
L19           10 "SCHWARTZ OLIVIER"/AU

=> d l19,ti,1-10

L19  ANSWER 1 OF 10      MEDLINE on STN
TI   DC-SIGN promotes exogenous MHC-I-restricted HIV-1 antigen presentation.

L19  ANSWER 2 OF 10      MEDLINE on STN
TI   Cell of the month. Dendritic cell sensing a lymphocyte.

L19  ANSWER 3 OF 10      MEDLINE on STN
TI   [HIV-1, a very Vif virus].
     VIH-1: un virus tres Vif !.

L19  ANSWER 4 OF 10      MEDLINE on STN
TI   DC-SIGN from African green monkeys is expressed in lymph nodes and
     mediates infection in trans of simian immunodeficiency virus SIVagm.

L19  ANSWER 5 OF 10      MEDLINE on STN
TI   The human polycomb group EED protein interacts with the integrase of human
     immunodeficiency virus type 1.

L19  ANSWER 6 OF 10      MEDLINE on STN
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productive infection of human dendritic cells by mosquito-cell-derived dengue viruses.

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L19  ANSWER 7 OF 10     MEDLINE on STN
TI   DC-SIGN and L-SIGN are high affinity binding receptors for hepatitis C
     virus glycoprotein E2.

L19  ANSWER 8 OF 10     MEDLINE on STN
TI   Inhibition of human immunodeficiency virus type 1 Env-mediated fusion by
     DC-SIGN.

L19  ANSWER 9 OF 10     MEDLINE on STN
TI   DC-SIGN is the major Mycobacterium tuberculosis receptor on human
     dendritic cells.

L19  ANSWER 10 OF 10     MEDLINE on STN
TI   HIV-1 Nef-induced upregulation of DC-SIGN in dendritic cells promotes
     lymphocyte clustering and viral spread.


=> s e3
L20          90 "SCHWARTZ O"/AU

=> s l20 and (DNA immun? or DNA vaccin? or gene vaccin? or DNA-based vaccin? or DNA-based immun
        740828 DNA
       1596286 IMMUN?
           840 DNA IMMUN?
                 (DNA(W)IMMUN?)
        740828 DNA
        146370 VACCIN?
          2145 DNA VACCIN?
                 (DNA(W)VACCIN?)
        679604 GENE
        146370 VACCIN?
            83 GENE VACCIN?
                 (GENE(W)VACCIN?)
        740828 DNA
        618515 BASED
        146370 VACCIN?
           140 DNA-BASED VACCIN?
                 (DNA(W)BASED(W)VACCIN?)
        740828 DNA
        618515 BASED
       1596286 IMMUN?
           130 DNA-BASED IMMUN?
                 (DNA(W)BASED(W)IMMUN?)
         54034 PLASMID
L21           2 L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BASED
               VACCIN? OR DNA-BASED IMMUN? OR PLASMID)

=> d l21,cbib,ab,1-2

L21  ANSWER 1 OF 2     MEDLINE on STN
```

2002354641. PubMed ID: 12097567. Enhanced presentation of major histocompatibility complex class I-restricted human immunodeficiency virus type 1 (HIV-1) Gag-specific epitopes after **DNA immunization** with vectors coding for vesicular stomatitis virus glycoprotein-pseudotyped HIV-1 Gag particles. Marsac D; Loirat D; Petit C; **Schwartz O**; Michel M-L. (Unite de Recombinaison et Expression Genetique, INSERM U.163, Institut Pasteur, 75724 Paris Cedex 15, France.) Journal of virology, (2002 Aug) 76 (15) 7544-53. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In vivo priming of cytotoxic T lymphocytes (CTL) by DNA injection predominantly occurs by antigen transfer from DNA-transfected cells to antigen-presenting cells. A rational strategy for increasing **DNA**

vaccine potency would be to use a delivery system that facilitates antigen uptake by antigen-presenting cells. Exogenous antigen presentation through the major histocompatibility complex (MHC) class I-restricted pathway of some viral antigens is increased after adequate virus-receptor interaction and the fusion of viral and cellular membranes. We used **DNA-based immunization** with plasmids coding for human immunodeficiency virus type 1 (HIV-1) Gag particles pseudotyped with vesicular stomatitis virus glycoprotein (VSV-G) to generate Gag-specific CTL responses. The presence of the VSV-G-encoding **plasmid** not only increased the number of mice displaying anti-Gag-specific cytotoxic response but also increased the efficiency of specific lysis. In vitro analysis of processing confirmed that exogenous presentation of Gag epitopes occurred much more efficiently when Gag particles were pseudotyped with the VSV-G envelope. We show that the VSV-G-pseudotyped Gag particles not only entered the MHC class II processing pathway but also entered the MHC class I processing pathway. In contrast, naked Gag particles entered the MHC class II processing pathway only. Thus, the combined use of **DNA-based immunization** and nonreplicating pseudotyped virus to deliver HIV-1 antigen to the immune system in vivo could be considered in HIV-1 vaccine design.

L21 ANSWER 2 OF 2 MEDLINE on STN

90269608. PubMed ID: 2189784. A microtransfection method using the luciferase-encoding reporter gene for the assay of human immunodeficiency virus LTR promoter activity. **Schwartz O**; Virelizier J L; Montagnier L; Hazan U. (Unite d'Oncologie Virale, Institut Pasteur, Paris, France.) Gene, (1990 Apr 16) 88 (2) 197-205. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB A microtransfection method, using either the DEAE-dextran or the Ca.phosphate procedure has been developed. A **plasmid** expressing the luciferase-encoding gene under the control of the human immunodeficiency virus (HIV) LTR promoter was constructed. Transfections were performed in 96-well plates, allowing statistical evaluation of the results. This microtransfection method requires the use of 100- to 1000-fold less **plasmid** and cells than in a conventional chloramphenicol acetyl transferase (CAT) assay. A Luciferase index which takes into account cell viability after transfection has been defined using a semi-automated absorbance assay. A 20-h incubation period post-transfection is sufficient for optimal results. Basal long terminal repeat activity and autologous Tat transactivation were studied in various lymphoid, monocytic and adherent human cell lines. Infection of microtransfected cells by HIV activated luc expression. This assay can thus also be used for rapid detection and quantitation of HIV. Antiviral activities of drugs can be assessed in a two-day test.

```
=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
```

```
L8             6 S E3
L9             5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                 E SCHWARTZ OLIVIER/IN
                 E SCHWARTZ O/IN
L10           16 S E3-E5
                 E BUSEYNE F/IN
L11            1 S E3
L12            0 S L11 NOT L10
                 E MARSAC D/IN
L13            2 S E3
L14            1 S L13 NOT L10
                 E RIVIERE Y/IN
L15            7 S E3 OR E4
L16            6 S L15 NOT L10
                 E HEARD J/IN
L17            2 S E8
L18            2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                 E SCHWARTZ O/AU
L19           10 S E7
L20           90 S E3
L21            2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS

=> d l20,ti,1-10

L20  ANSWER 1 OF 90     MEDLINE on STN
TI   Commonsense design of patella implant: four years of clinical experience
     with 124 patients.

L20  ANSWER 2 OF 90     MEDLINE on STN
TI   Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of
     the femoral head.

L20  ANSWER 3 OF 90     MEDLINE on STN
TI   Effects of temperature, storage time and media on periodontal and pulpal
     healing after replantation of incisors in monkeys.

L20  ANSWER 4 OF 90     MEDLINE on STN
TI   Allo- and autotransplantation of mature teeth in monkeys: a sequential
     time-related histoquantitative study of periodontal and pulpal healing.

L20  ANSWER 5 OF 90     MEDLINE on STN
TI   A comparative biomechanical study of the strength of the bony patella
     following dome cut or uniplanar cut in total knee arthroplasty.

L20  ANSWER 6 OF 90     MEDLINE on STN
TI   Wear pattern of retrieved patellar implants.

L20  ANSWER 7 OF 90     MEDLINE on STN
TI   Effect of treatment delay upon pulp and periodontal healing of traumatic
     dental injuries -- a review article.

L20  ANSWER 8 OF 90     MEDLINE on STN
TI   Enhanced presentation of major histocompatibility complex class
     I-restricted human immunodeficiency virus type 1 (HIV-1) Gag-specific
     epitopes after DNA immunization with vectors coding for vesicular
     stomatitis virus glycoprotein-pseudotyped HIV-1 Gag particles.

L20  ANSWER 9 OF 90     MEDLINE on STN
TI   Production and neurotropism of lentivirus vectors pseudotyped with
     lyssavirus envelope glycoproteins.
```

TI HIV-1 Nef impairs MHC class II antigen presentation and surface expression.

=> d l20,ti,11-20

L20 ANSWER 11 OF 90 MEDLINE on STN
TI Human immunodeficiency virus type 1 entry into macrophages mediated by macropinocytosis.

L20 ANSWER 12 OF 90 MEDLINE on STN
TI Complications of K-wire fixation of fractures and dislocations in the hand and wrist.

L20 ANSWER 13 OF 90 MEDLINE on STN
TI Natural signal statistics and sensory gain control.

L20 ANSWER 14 OF 90 MEDLINE on STN
TI Nef is required for efficient HIV-1 replication in cocultures of dendritic cells and lymphocytes.

L20 ANSWER 15 OF 90 MEDLINE on STN
TI HIV auxiliary proteins: an interface between the virus and the host.

L20 ANSWER 16 OF 90 MEDLINE on STN
TI MHC-I-restricted presentation of HIV-1 virion antigens without viral replication.

L20 ANSWER 17 OF 90 MEDLINE on STN
TI Nef-induced CD4 downregulation: a diacidic sequence in human immunodeficiency virus type 1 Nef does not function as a protein sorting motif through direct binding to beta-COP.

L20 ANSWER 18 OF 90 MEDLINE on STN
TI Distinct trafficking pathways mediate Nef-induced and clathrin-dependent major histocompatibility complex class I down-regulation.

L20 ANSWER 19 OF 90 MEDLINE on STN
TI The karyophilic properties of human immunodeficiency virus type 1 integrase are not required for nuclear import of proviral DNA.

L20 ANSWER 20 OF 90 MEDLINE on STN
TI Mutation of a conserved residue (D123) required for oligomerization of human immunodeficiency virus type 1 Nef protein abolishes interaction with human thioesterase and results in impairment of Nef biological functions.

=>
=> d l20,cbib,ab,16

L20 ANSWER 16 OF 90 MEDLINE on STN
2001198778. PubMed ID: 11231634. MHC-I-restricted presentation of HIV-1 virion antigens without viral replication. Buseyne F; Le Gall S; Boccaccio C; Abastado J P; Lifson J D; Arthur L O; Riviere Y; Heard J M; **Schwartz O.** (Laboratoire d'Immunopathologie Viralem, Institut Pasteur, Paris, France.) Nature medicine, (2001 Mar) 7 (3) 344-9. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Dendritic cells and macrophages can process extracellular antigens for presentation by MHC-I molecules. This exogenous pathway may have a crucial role in the activation of CD8+ cytotoxic T lymphocytes during human viral infections. We show here that HIV-1 epitopes derived from incoming virions are presented through the exogenous MHC-I pathway in primary human dendritic cells, and to a lower extent in macrophages, leading to cytotoxic T-lymphocyte activation in the absence of viral protein synthesis. Exogenous antigen presentation required adequate

virus-receptor interactions and fusion of viral and cellular membranes.
These results provide new insights into how anti-HIV cytotoxic T
lymphocytes can be activated and have implications for anti-HIV vaccine
design.

=> d l20,ti,21-30

L20 ANSWER 21 OF 90 MEDLINE on STN
TI Combined immunofluorescence and field emission scanning electron
microscope study of plasma membrane-associated organelles in highly
vacuolated suspensor cells of white spruce somatic embryos.

L20 ANSWER 22 OF 90 MEDLINE on STN
TI The downregulation of CD4 and MHC-I by primate lentiviruses: a paradigm
for the modulation of cell surface receptors.

L20 ANSWER 23 OF 90 MEDLINE on STN
TI Oligomerization within virions and subcellular localization of human
immunodeficiency virus type 1 integrase.

L20 ANSWER 24 OF 90 MEDLINE on STN
TI Traumatic injuries of the teeth in connection with general anaesthesia and
the effect of use of mouthguards.

L20 ANSWER 25 OF 90 MEDLINE on STN
TI Opposite effects of SDF-1 on human immunodeficiency virus type 1
replication.

L20 ANSWER 26 OF 90 MEDLINE on STN
TI Nef interacts with the mu subunit of clathrin adaptor complexes and
reveals a cryptic sorting signal in MHC I molecules.

L20 ANSWER 27 OF 90 MEDLINE on STN
TI Antiviral activity of the proteasome on incoming human immunodeficiency
virus type 1.

L20 ANSWER 28 OF 90 MEDLINE on STN
TI Cytosolic Gag p24 as an index of productive entry of human
immunodeficiency virus type 1.

L20 ANSWER 29 OF 90 MEDLINE on STN
TI Positive association of the beta fibrinogen H1/H2 gene variation to basal
fibrinogen levels and to the increase in fibrinogen concentration during
acute phase reaction but not to coronary artery disease and myocardial
infarction.

L20 ANSWER 30 OF 90 MEDLINE on STN
TI HIV coreceptor downregulation as antiviral principle: SDF-1alpha-dependent
internalization of the chemokine receptor CXCR4 contributes to inhibition
of HIV replication.

=> d l20,ti,31-50

L20 ANSWER 31 OF 90 MEDLINE on STN
TI Binding of HIV-1 Nef to a novel thioesterase enzyme correlates with
Nef-mediated CD4 down-regulation.

L20 ANSWER 32 OF 90 MEDLINE on STN
TI Human immunodeficiency virus type I Nef independently affects virion
incorporation of major histocompatibility complex class I molecules and
virus infectivity.

L20 ANSWER 33 OF 90 MEDLINE on STN
TI Analysis of Nef-induced MHC-I endocytosis.

L20 ANSWER 34 OF 90 MEDLINE on STN
TI The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1.

L20 ANSWER 35 OF 90 MEDLINE on STN
TI A cell surface marker gene transferred with a retroviral vector into CD34+ cord blood cells is expressed by their T-cell progeny in the SCID-hu thymus.

L20 ANSWER 36 OF 90 MEDLINE on STN
TI Endocytosis of major histocompatibility complex class I molecules is induced by the HIV-1 Nef protein.

L20 ANSWER 37 OF 90 MEDLINE on STN
TI Pulp and periodontal healing, root development and root resorption subsequent to transplantation and orthodontic rotation: a long-term study of autotransplanted premolars.

L20 ANSWER 38 OF 90 MEDLINE on STN
TI Gene polymorphism but not catalytic activity of angiotensin I-converting enzyme is associated with coronary artery disease and myocardial infarction in low-risk patients.

L20 ANSWER 39 OF 90 MEDLINE on STN
TI Human immunodeficiency virus type 1 Nef increases the efficiency of reverse transcription in the infected cell.

L20 ANSWER 40 OF 90 MEDLINE on STN
TI Human immunodeficiency virus type 1 Nef induces accumulation of CD4 in early endosomes.

L20 ANSWER 41 OF 90 MEDLINE on STN
TI Efficient antigen presentation to cytotoxic T lymphocytes by cells transduced with a retroviral vector expressing the HIV-1 Nef protein.

L20 ANSWER 42 OF 90 MEDLINE on STN
TI Impairment of T cell receptor-dependent stimulation in CD4+ lymphocytes after contact with membrane-bound HIV-1 envelope glycoprotein.

L20 ANSWER 43 OF 90 MEDLINE on STN
TI Reduced cell surface expression of processed human immunodeficiency virus type 1 envelope glycoprotein in the presence of Nef.

L20 ANSWER 44 OF 90 MEDLINE on STN
TI Activation pathways and human immunodeficiency virus type 1 replication are not altered in CD4+ T cells expressing the nef protein.

L20 ANSWER 45 OF 90 MEDLINE on STN
TI Architectural organization of human oral epithelium as visualized by keratin staining pattern in tobacco-associated leukoplakias.

L20 ANSWER 46 OF 90 MEDLINE on STN
TI Lipophilic glycosyl phosphotriester derivatives of AZT: synthesis, NMR transmembrane transport study, and antiviral activity.

L20 ANSWER 47 OF 90 MEDLINE on STN
TI Reinnervation of autotransplanted teeth. A histological investigation in monkeys.

L20 ANSWER 48 OF 90 MEDLINE on STN
TI [Carcinoma in situ of soft palate].
Carcinoma in situ i den blode gane.

L20 ANSWER 49 OF 90 MEDLINE on STN
TI [Treatment of anterior tooth loss by autotransplantation of premolars].

L20 ANSWER 50 OF 90 MEDLINE on STN
TI Transmission electron microscopy of supra-alveolar periodontal healing of
auto- and allotransplanted teeth in monkeys.

=> d l20,cbib,ab,41

L20 ANSWER 41 OF 90 MEDLINE on STN
94190626. PubMed ID: 7511396. Efficient antigen presentation to cytotoxic T lymphocytes by cells transduced with a retroviral vector expressing the HIV-1 Nef protein. Robertson M N; Buseyne F; **Schwartz O**; Riviere Y. (Unite de Virologie et Immunologie Cellulaire, Institut Pasteur, Paris.) AIDS research and human retroviruses, (1993 Dec) 9 (12) 1217-23. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB In the classic model of antigen processing and presentation, viral antigens must be synthesized within the cytoplasm of infected cells to be processed and presented to CD8+, MHC class I-restricted cytotoxic T lymphocytes (CTLs). We have examined the utility of a retroviral vector (pNeoNef) expressing the human immunodeficiency virus type (HIV-1)Lai Nef protein for the development of target cells to study HIV-specific CTLs. Autologous Epstein-Barr-transformed B cell lines (EBV-B cells) transduced with pNeoNef were efficiently lysed by CTL lines from donors capable of lysing EBV-B cells infected with a recombinant vaccinia virus (rVV) expressing Nef. Also, the transduced cells were efficient stimulator cells for the generation of Nef-specific CTL lines. The CTL lines thus generated recognized the same epitopes as CTL lines from the same donor generated by nonspecific stimulation. The use of similar cell lines transduced with retroviral vectors expressing HIV proteins may be useful in the study of CTLs in HIV-infected donors and in the study of the ability of candidate vaccines, including rVV, to induce HIV-specific CTLs. As antigen-presenting cells, the cell lines may be useful in the generation of antigen-specific CTL lines.

=> d l20,ti,51-75

L20 ANSWER 51 OF 90 MEDLINE on STN
TI Export and one-step purification from Escherichia coli of a MalE-CD4
hybrid protein that neutralizes HIV in vitro.

L20 ANSWER 52 OF 90 MEDLINE on STN
TI Supra-alveolar periodontal healing of auto- and allotransplanted teeth in
monkeys.

L20 ANSWER 53 OF 90 MEDLINE on STN
TI A microtransfection method using the luciferase-encoding reporter gene for
the assay of human immunodeficiency virus LTR promoter activity.

L20 ANSWER 54 OF 90 MEDLINE on STN
TI Tooth exfoliation and necrosis of the alveolar bone following trigeminal
herpes zoster in HIV-infected patient.

L20 ANSWER 55 OF 90 MEDLINE on STN
TI A long-term study of 370 autotransplanted premolars. Part I. Surgical
procedures and standardized techniques for monitoring healing.

L20 ANSWER 56 OF 90 MEDLINE on STN
TI A long-term study of 370 autotransplanted premolars. Part III. Periodontal
healing subsequent to transplantation.

L20 ANSWER 57 OF 90 MEDLINE on STN
TI A long-term study of 370 autotransplanted premolars. Part II. Tooth
survival and pulp healing subsequent to transplantation.

L20 ANSWER 58 OF 90 MEDLINE on STN
TI [Neutralising properties for HIV virus of hybrid protein MalE-CD4 expressed in E. coli and purified in 1 step].
Proprietes neutralisantes pour le virus HIV d'une proteine hybride MalE-CD4 exprimee chez E. coli et purifiable en une etape.

L20 ANSWER 59 OF 90 MEDLINE on STN
TI A rapid and simple colorimetric test for the study of anti-HIV agents.

L20 ANSWER 60 OF 90 MEDLINE on STN
TI Allotransplantation and autotransplantation of mature teeth in monkeys: the influence of endodontic treatment.

L20 ANSWER 61 OF 90 MEDLINE on STN
TI [Particles with retrovirus appearance and reverse transcriptase activity in cell cultures derived from lymph node biopsies in Hodgkin's disease].
Particules d'aspect retroviral et activite transcriptase inverse dans des cultures cellulaires derivees de biopsies ganglionnaires de malade de Hodgkin.

L20 ANSWER 62 OF 90 MEDLINE on STN
TI Allotransplantation of human teeth. A retrospective study of 73 transplantations over a period of 28 years.

L20 ANSWER 63 OF 90 MEDLINE on STN
TI Tooth transplantation to bone graft in cleft alveolus.

L20 ANSWER 64 OF 90 MEDLINE on STN
TI [Bone reconstruction of mandibular defects with and without continuity defects].
Ossos rekonstruktion af underkaebedefekter med og uden kontinuitetsafbrydelse.

L20 ANSWER 65 OF 90 MEDLINE on STN
TI [Reconstruction of alveolar process in a cases of cleft lip, jaw and palate].
Rekonstruktion af procesus alveolaris ved laebe-kaebe-ganespalte.

L20 ANSWER 66 OF 90 MEDLINE on STN
TI Autotransplantation of cryopreserved tooth in connection with orthodontic treatment.

L20 ANSWER 67 OF 90 MEDLINE on STN
TI Indications for surgical removal of supernumerary teeth in the premaxilla.

L20 ANSWER 68 OF 90 MEDLINE on STN
TI The effect of saline storage before replantation upon dry damage of the periodontal ligament.

L20 ANSWER 69 OF 90 MEDLINE on STN
TI Cryopreservation as long-term storage of teeth for transplantation or replantation.

L20 ANSWER 70 OF 90 MEDLINE on STN
TI Langerhans cells in candidal leukoplakia.

L20 ANSWER 71 OF 90 MEDLINE on STN
TI Cryopreservation before replantation of mature teeth in monkeys. (II). Effect of preincubation, different freezing and equilibration rates and endodontic treatment upon periodontal healing.

L20 ANSWER 72 OF 90 MEDLINE on STN
TI Autotransplantation of human teeth. A life-table analysis of prognostic factors.

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L20  ANSWER 73 OF 90     MEDLINE on STN
TI   Resorption of autotransplanted human teeth: a retrospective study of 291
     transplantations over a period of 25 years.

L20  ANSWER 74 OF 90     MEDLINE on STN
TI   The effect of apicoectomy before replantation on periodontal and pulpal
     healing in teeth in monkeys.

L20  ANSWER 75 OF 90     MEDLINE on STN
TI   Cryopreservation of mature teeth before replantation in monkeys (I).
     Effect of different cryoprotective agents and freezing devices.


=> e buseyne f/au
E1             3     BUSEY W/AU
E2            22     BUSEY W M/AU
E3            22 --> BUSEYNE F/AU
E4             3     BUSEYNE FLORENCE/AU
E5             3     BUSFIELD B L JR/AU
E6            16     BUSFIELD D/AU
E7            10     BUSFIELD F/AU
E8             2     BUSFIELD FRANCES/AU
E9             1     BUSFIELD G/AU
E10            5     BUSFIELD J/AU
E11            2     BUSFIELD JOAN/AU
E12            3     BUSFIELD P I/AU

=> s e3 or e4
              22 "BUSEYNE F"/AU
               3 "BUSEYNE FLORENCE"/AU
L22           25 "BUSEYNE F"/AU OR "BUSEYNE FLORENCE"/AU

=> s l22 not l20
L23           21 L22 NOT L20

=> d l23,ti,1-21

L23  ANSWER 1 OF 21     MEDLINE on STN
TI   DC-SIGN promotes exogenous MHC-I-restricted HIV-1 antigen presentation.

L23  ANSWER 2 OF 21     MEDLINE on STN
TI   Inverse correlation between memory Gag-specific cytotoxic T lymphocytes
     and viral replication in human immunodeficiency virus-infected children.

L23  ANSWER 3 OF 21     MEDLINE on STN
TI   Frequencies of ex vivo-activated human immunodeficiency virus type
     1-specific gamma-interferon-producing CD8+ T cells in infected children
     correlate positively with plasma viral load.

L23  ANSWER 4 OF 21     MEDLINE on STN
TI   Design of a polyepitope construct for the induction of
     HLA-A0201-restricted HIV 1-specific CTL responses using HLA-A*0201
     transgenic, H-2 class I KO mice.

L23  ANSWER 5 OF 21     MEDLINE on STN
TI   The flexibility of the TCR allows recognition of a large set of naturally
     occurring epitope variants by HIV-specific cytotoxic T lymphocytes.

L23  ANSWER 6 OF 21     MEDLINE on STN
TI   Frequency and phenotyping of human immunodeficiency virus (HIV)-specific
     CD8+ T cells in HIV-infected children, using major histocompatibility
     complex class I peptide tetramers.

L23  ANSWER 7 OF 21     MEDLINE on STN
TI   Patient-specific cytotoxic T-lymphocyte cross-recognition of naturally
     occurring variants of a human immunodeficiency virus type 1 (HIV-1) p24gag
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epitope by HIV-1 infected children.

L23 ANSWER 8 OF 21 MEDLINE on STN
TI Early HIV-specific cytotoxic T lymphocytes and disease progression in children born to HIV-infected mothers.

L23 ANSWER 9 OF 21 MEDLINE on STN
TI Impact of heterozygosity for the chemokine receptor CCR5 32-bp-deleted allele on plasma virus load and CD4 T lymphocytes in perinatally human immunodeficiency virus-infected children at 8 years of age.

L23 ANSWER 10 OF 21 MEDLINE on STN
TI Cross-clade-specific cytotoxic T lymphocytes in HIV-1-infected children.

L23 ANSWER 11 OF 21 MEDLINE on STN
TI Cytotoxic T lymphocytes generation capacity in early life with particular reference to HIV.

L23 ANSWER 12 OF 21 MEDLINE on STN
TI Characterization of an HIV-1 p24gag epitope recognized by a CD8+ cytotoxic T-cell clone.

L23 ANSWER 13 OF 21 MEDLINE on STN
TI Dual function of a human immunodeficiency virus (HIV)-specific cytotoxic T-lymphocyte clone: inhibition of HIV replication by noncytolytic mechanisms and lysis of HIV-infected CD4+ cells.

L23 ANSWER 14 OF 21 MEDLINE on STN
TI Memory cytotoxic T lymphocyte responses in human immunodeficiency virus type 1 (HIV-1)-negative volunteers immunized with a recombinant canarypox expressing gp 160 of HIV-1 and boosted with a recombinant gp160.

L23 ANSWER 15 OF 21 MEDLINE on STN
TI Cytotoxic T lymphocytes in human immunodeficiency virus infection: regulator genes.

L23 ANSWER 16 OF 21 MEDLINE on STN
TI Multispecific and heterogeneous recognition of the gag protein by cytotoxic T lymphocytes (CTL) from HIV-infected patients: factors other than the MHC control the epitopic specificities.

L23 ANSWER 17 OF 21 MEDLINE on STN
TI HIV-specific CD8+ T-cell immune responses and viral replication.

L23 ANSWER 18 OF 21 MEDLINE on STN
TI Strain specificity of cell-mediated cytotoxic responses specific for the human immunodeficiency virus type 1 (HIV-1) envelope protein in seropositive donors: HIV-1Lai is more commonly recognized than HIV-1MN.

L23 ANSWER 19 OF 21 MEDLINE on STN
TI Detection of HIV-specific cell-mediated cytotoxicity in the peripheral blood from infected children.

L23 ANSWER 20 OF 21 MEDLINE on STN
TI Gag-specific cytotoxic T lymphocytes from human immunodeficiency virus type 1-infected individuals: Gag epitopes are clustered in three regions of the p24gag protein.

L23 ANSWER 21 OF 21 MEDLINE on STN
TI [The cellular immunity response to the gag protein of HIV-1].
La reponse immunitaire cellulaire contre la proteine gag de VIH-1.

=> d l23,cbib,ab,1,14

L23 ANSWER 1 OF 21 MEDLINE on STN

MHC-I-restricted HIV-1 antigen presentation. Moris Arnaud; Nobile Cinzia; **Buseyne Florence**; Porrot Francoise; Abastado Jean-Pierre; Schwartz Olivier. (Groupe Virus et Immunite, URA CNRS 1930, Institut Pasteur, Paris, France.) Blood, (2004 Apr 1) 103 (7) 2648-54. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) facilitate HIV-1 spread in the host by capturing virions and transferring them to permissive lymphocytes in lymphoid organs. Lectins such as DC-specific ICAM-grabbing non-integrin (DC-SIGN) are involved in HIV-1 uptake by DCs, through high-affinity binding to viral envelope glycoproteins. We examined the role of DC-SIGN on the fate of incoming virions and on major histocompatibility complex class I (MHC-I)-restricted HIV-1 antigen presentation. We show that DC-SIGN expression in B-cell lines dramatically enhances viral internalization. In these cells, and also in primary DCs, most of the captured virions are rapidly degraded, likely in a lysosomal compartment. In addition, a fraction of incoming viral material is processed by the proteasome, leading to activation of anti-HIV-specific cytotoxic T lymphocytes (CTLs) by DC-SIGN-expressing cells. In DCs, DC-SIGN is not the only receptor involved, and redundant pathways of virus capture leading to antigen presentation likely coexist. Altogether, our results highlight new aspects of DC-SIGN interactions with HIV-1. The lectin does not significantly protect captured virions against degradation and promotes MHC-I exogenous presentation of HIV-1 antigens.

L23 ANSWER 14 OF 21 MEDLINE on STN

97000067. PubMed ID: 8843210. Memory cytotoxic T lymphocyte responses in human immunodeficiency virus type 1 (HIV-1)-negative volunteers immunized with a recombinant canarypox expressing gp 160 of HIV-1 and boosted with a recombinant gp160. Fleury B; Janvier G; Pialoux G; **Buseyne F**; Robertson M N; Tartaglia J; Paoletti E; Kieny M P; Excler J L; Riviere Y. (Unite de Virologie et Immunologie Cellulaire, Institut Pasteur, Paris, France.) Journal of infectious diseases, (1996 Oct) 174 (4) 734-8. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB A vaccine against human immunodeficiency virus (HIV) should induce virus-specific cytotoxic T lymphocyte (CTL) activity. Immunization of uninfected volunteers with a canarypox virus expressing HIV envelope was carried out in a phase I trial. Two injections of canarypox expressing HIV-1MN gp 160 (months 0 and 1) were followed by two boosts of recombinant envelope protein (months 3 and 6). HIV envelope-specific CTL were detected in peripheral blood mononuclear cells stimulated with autologous HIV-1-infected blast cells. T cell lines were obtained from 18 of 20 donors: CTL were detected at least once following immunization in 7 (39%) of these 18. This activity was mediated by major histocompatibility complex class I-restricted CD3+CD8+ T cells. For two subjects, this activity was still present 2 years after the initial immunization. The CTL responses with this prime-boost regimen are the best observed with any HIV vaccine tested in humans.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
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                  E RIVIERE YVES/IN
L6              2 S E3
L7              1 S L6 NOT L1
                  E HEARD JEAN MICHEL/IN
L8              6 S E3
L9              5 S L8 NOT L1

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                  E SCHWARTZ OLIVIER/IN
                  E SCHWARTZ O/IN
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                  E BUSEYNE F/IN
L11             1 S E3
L12             0 S L11 NOT L10
                  E MARSAC D/IN
L13             2 S E3
L14             1 S L13 NOT L10
                  E RIVIERE Y/IN
L15             7 S E3 OR E4
L16             6 S L15 NOT L10
                  E HEARD J/IN
L17             2 S E8
L18             2 S L17 NOT L10

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                  E SCHWARTZ O/AU
L19            10 S E7
L20            90 S E3
L21             2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                  E BUSEYNE F/AU
L22            25 S E3 OR E4
L23            21 S L22 NOT L20

=> e marsac e/au
E1             7      MARSAC CECILE/AU
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E3             0 -->  MARSAC E/AU
E4             1      MARSAC G/AU
E5           106      MARSAC J/AU
E6             7      MARSAC J H/AU
E7             1      MARSACK C R/AU
E8             1      MARSACK J D/AU
E9             1      MARSACK JASON/AU
E10            1      MARSACK JASON D/AU
E11            1      MARSACK K Z/AU
E12            4      MARSACK P/AU

=> s e2
L24            1 "MARSAC D"/AU

=> s l24 not l20
L25            0 L24 NOT L20

=> e riviere y/au
E1             4      RIVIERE THERET T M/AU
E2             3      RIVIERE V/AU
E3            97 -->  RIVIERE Y/AU
E4             7      RIVIERE YVES/AU
E5             1      RIVIERES R/AU
E6             3      RIVIEREZ E/AU
E7             2      RIVIEREZ J A/AU
E8            38      RIVIEREZ M/AU
E9             1      RIVIEREZ MAURICE/AU
E10            1      RIVIERI F/AU
E11            1      RIVIERRE ARMELLE/AU
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=> s e3 or e4
             97 "RIVIERE Y"/AU
              7 "RIVIERE YVES"/AU
L26         104 "RIVIERE Y"/AU OR "RIVIERE YVES"/AU

=> s l26 not l20
L27         101 L26 NOT L20

=> d l27,ti,1-25

L27  ANSWER 1 OF 101     MEDLINE on STN
TI   Kinetics of lymphocyte proliferation during primary immune response in
     macaques infected with pathogenic simian immunodeficiency virus SIVmac251:
     preliminary report of the effect of early antiviral therapy.

L27  ANSWER 2 OF 101     MEDLINE on STN
TI   Extensive apoptosis in lymphoid organs during primary SIV infection
     predicts rapid progression towards AIDS.

L27  ANSWER 3 OF 101     MEDLINE on STN
TI   Markov modelling of changes in HIV-specific cytotoxic T-lymphocyte
     responses with time in untreated HIV-1 infected patients.

L27  ANSWER 4 OF 101     MEDLINE on STN
TI   Early and late cytotoxic T lymphocyte responses in HIV infection.

L27  ANSWER 5 OF 101     MEDLINE on STN
TI   Correlation between breadth of memory HIV-specific cytotoxic T cells,
     viral load and disease progression in HIV infection.

L27  ANSWER 6 OF 101     MEDLINE on STN
TI   Inverse correlation between memory Gag-specific cytotoxic T lymphocytes
     and viral replication in human immunodeficiency virus-infected children.

L27  ANSWER 7 OF 101     MEDLINE on STN
TI   Frequencies of ex vivo-activated human immunodeficiency virus type
     1-specific gamma-interferon-producing CD8+ T cells in infected children
     correlate positively with plasma viral load.

L27  ANSWER 8 OF 101     MEDLINE on STN
TI   Lack of an immune response against the tetracycline-dependent
     transactivator correlates with long-term doxycycline-regulated transgene
     expression in nonhuman primates after intramuscular injection of
     recombinant adeno-associated virus.

L27  ANSWER 9 OF 101     MEDLINE on STN
TI   Design of a polyepitope construct for the induction of
     HLA-A0201-restricted HIV 1-specific CTL responses using HLA-A*0201
     transgenic, H-2 class I KO mice.

L27  ANSWER 10 OF 101     MEDLINE on STN
TI   A long-term follow-up of an HIV type 1-infected patient reveals a
     coincidence of Nef-directed cytotoxic T lymphocyte effectors and high
     incidence of epitope-deleted variants.

L27  ANSWER 11 OF 101     MEDLINE on STN
TI   Expansion of HBV-specific memory CTL primed by dual HIV/HBV genetic
     immunization during SHIV primary infection in rhesus macaques.

L27  ANSWER 12 OF 101     MEDLINE on STN
TI   The flexibility of the TCR allows recognition of a large set of naturally
     occurring epitope variants by HIV-specific cytotoxic T lymphocytes.

L27  ANSWER 13 OF 101     MEDLINE on STN
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CD8+ T cells in HIV-infected children, using major histocompatibility complex class I peptide tetramers.

L27 ANSWER 14 OF 101 MEDLINE on STN
TI A novel flow cytometric assay for quantitation and multiparametric characterization of cell-mediated cytotoxicity.

L27 ANSWER 15 OF 101 MEDLINE on STN
TI Patient-specific cytotoxic T-lymphocyte cross-recognition of naturally occurring variants of a human immunodeficiency virus type 1 (HIV-1) p24gag epitope by HIV-1-infected children.

L27 ANSWER 16 OF 101 MEDLINE on STN
TI Immune responses following simian/human immunodeficiency virus (SHIV) challenge of rhesus macaques after human immunodeficiency virus (HIV)-1 third variable domain (V3) loop-based genetic immunization.

L27 ANSWER 17 OF 101 MEDLINE on STN
TI CD8(+)-Cell antiviral factor activity is not restricted to human immunodeficiency virus (HIV)-specific T cells and can block HIV replication after initiation of reverse transcription.

L27 ANSWER 18 OF 101 MEDLINE on STN
TI Implication of the C-terminal domain of nef protein in the reversion to pathogenicity of attenuated SIVmacBK28-41 in macaques.

L27 ANSWER 19 OF 101 MEDLINE on STN
TI Combined genotypes of CCR5, CCR2, SDF1, and HLA genes can predict the long-term nonprogressor status in human immunodeficiency virus-1-infected individuals.

L27 ANSWER 20 OF 101 MEDLINE on STN
TI Early HIV-specific cytotoxic T lymphocytes and disease progression in children born to HIV-infected mothers.

L27 ANSWER 21 OF 101 MEDLINE on STN
TI Impact of heterozygosity for the chemokine receptor CCR5 32-bp-deleted allele on plasma virus load and CD4 T lymphocytes in perinatally human immunodeficiency virus-infected children at 8 years of age.

L27 ANSWER 22 OF 101 MEDLINE on STN
TI Cross-clade-specific cytotoxic T lymphocytes in HIV-1-infected children.

L27 ANSWER 23 OF 101 MEDLINE on STN
TI Cytotoxic T lymphocytes generation capacity in early life with particular reference to HIV.

L27 ANSWER 24 OF 101 MEDLINE on STN
TI In vivo induction of specific cytotoxic T lymphocytes in mice and rhesus macaques immunized with DNA vector encoding an HIV epitope fused with hepatitis B surface antigen.

L27 ANSWER 25 OF 101 MEDLINE on STN
TI CD26 as a positive regulator of HIV envelope-glycoprotein induced apoptosis in CD4+ T cells.

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=> d l27,cbib,ab,5,24

L27 ANSWER 5 OF 101 MEDLINE on STN
2002698750. PubMed ID: 12461413. Correlation between breadth of memory HIV-specific cytotoxic T cells, viral load and disease progression in HIV infection. Chouquet Cecile; Autran Brigitte; Gomard Elisabeth; Bouley Jean-Marc; Calvez Vincent; Katlama Christine; Costagliola Dominique;

Tissulaire, Centre Hospitalier Pitie-Salpetriere, Institut Pasteur, 25 rue du Dr. Roux, 75015 Paris, France. (IMMUNOCO Study Group).) AIDS (London, England), (2002 Dec 6) 16 (18) 2399-407. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Memory cytotoxic T lymphocytes (CTL) should play a key role in controlling HIV infection. The correlations between the breadth and specificities of memory CTL and virus production and disease progression are still unknown, but are of major importance for vaccine strategies. METHODS AND DESIGN: One-hundred and forty-eight chronically-infected patients, enrolled before the advent of highly active antiretroviral therapy, were followed-up prospectively over 5 years. Memory CTL were tested in vitro against autologous target cells expressing Env, Gag, Pol, Nef, Vif, Rev or Tat HIV-LAI sequences. RESULTS: At entry, an HIV-specific CTL response was detected against at least one viral protein in 77% cases, with Pol and Gag recognized in 57% each, Env and Nef in 36% and 30%, Vif, Rev and Tat in 14%, 10% and 5% of cases respectively. The same pattern was observed over time with some individual variations in responder status. Multivariate analysis of longitudinal data showed that the average number of recognized proteins of two at entry significantly decreased over time with the average loss of one protein per 7 years. The number of recognized proteins was negatively associated with viral load (P < 0.05), and with occurrence of opportunistic infection (P < 0.01), and significantly correlated with CD8 cell counts (P < 0.05) but not with CD4 cell counts. CONCLUSION: The breadth of HIV antigens recognized by memory CTL is a major correlate of immune control of HIV-replication and disease progression.

L27 ANSWER 24 OF 101 MEDLINE on STN

1998118456. PubMed ID: 9454704. In vivo induction of specific cytotoxic T lymphocytes in mice and rhesus macaques immunized with DNA vector encoding an HIV epitope fused with hepatitis B surface antigen. Le Borgne S; Mancini M; Le Grand R; Schleef M; Dormont D; Tiollais P; **Riviere Y**; Michel M L. (Unite de Virologie et Immunologie Cellulaire, URA CNRS 1157, Paris, France.) Virology, (1998 Jan 20) 240 (2) 304-15. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB DNA immunization offers a novel means to induce humoral and cellular immunity in inbred or in outbred animals. Here we have tested the efficiency of genetic immunization with hepatitis B virus (HBV) envelope-based vectors. In naive primates, injection of a plasmid DNA encoding HBV envelope proteins induced an HBV-specific cytotoxic response and appearance of potentially protective anti-HBs antibodies. Moreover, intramuscular and intradermal injections of a DNA expression vector encoding an epitope of the human immunodeficiency virus envelope fused to the surface protein of the hepatitis B virus (HBsAg) induced strong humoral and cytotoxic responses to antigenic determinants of both viruses in mice and nonhuman primates alike. In addition, in protein-primed Rhesus monkeys B-cell memory was successfully boosted by DNA injection of hybrid vectors and animals subsequently developed a multispecific cellular response. This suggests that DNA-based immunization could be used to boost efficiently and broaden the immune response in individuals immunized with conventional vaccines, regardless of their genetic variability. These results also indicate that it might be possible to rationally design HBsAg-based expression vectors to induce multispecific immune responses for vaccination against hepatitis B and other pathogens.

=> d l27,ti,26-50

L27 ANSWER 26 OF 101 MEDLINE on STN

TI Potential deleterious effect of anti-viral cytotoxic lymphocyte through the CD95 (FAS/APO-1)-mediated pathway during chronic HIV infection.

L27 ANSWER 27 OF 101 MEDLINE on STN

TI Characterization of an HIV-1 p24gag epitope recognized by a CD8+ cytotoxic T-cell clone.

L27 ANSWER 28 OF 101 MEDLINE on STN
TI Dual function of a human immunodeficiency virus (HIV)-specific cytotoxic T-lymphocyte clone: inhibition of HIV replication by noncytolytic mechanisms and lysis of HIV-infected CD4+ cells.

L27 ANSWER 29 OF 101 MEDLINE on STN
TI Memory cytotoxic T lymphocyte responses in human immunodeficiency virus type 1 (HIV-1)-negative volunteers immunized with a recombinant canarypox expressing gp 160 of HIV-1 and boosted with a recombinant gp160.

L27 ANSWER 30 OF 101 MEDLINE on STN
TI HIV envelope glycoprotein-induced cell killing by apoptosis is enhanced with increased expression of CD26 in CD4+ T cells.

L27 ANSWER 31 OF 101 MEDLINE on STN
TI Gag-specific cytotoxic responses to HIV type 1 are associated with a decreased risk of progression to AIDS-related complex or AIDS.

L27 ANSWER 32 OF 101 MEDLINE on STN
TI Heterologous HIV-2 challenge of rhesus monkeys immunized with recombinant vaccinia viruses and purified recombinant HIV-2 proteins.

L27 ANSWER 33 OF 101 MEDLINE on STN
TI A prime-boost approach to HIV preventive vaccine using a recombinant canarypox virus expressing glycoprotein 160 (MN) followed by a recombinant glycoprotein 160 (MN/LAI). The AGIS Group, and l'Agence Nationale de Recherche sur le SIDA.

L27 ANSWER 34 OF 101 MEDLINE on STN
TI Sequence constraints and recognition by CTL of an HLA-B27-restricted HIV-1 gag epitope.

L27 ANSWER 35 OF 101 MEDLINE on STN
TI Virus-specific cytotoxic T lymphocyte responses in patients infected with the human immunodeficiency virus, HIV-1.

L27 ANSWER 36 OF 101 MEDLINE on STN
TI Cytotoxic T lymphocytes in human immunodeficiency virus infection: regulator genes.

L27 ANSWER 37 OF 101 MEDLINE on STN
TI Vaccine-induced neutralizing antibodies directed in part to the simian immunodeficiency virus (SIV) V2 domain were unable to protect rhesus monkeys from SIV experimental challenge.

L27 ANSWER 38 OF 101 MEDLINE on STN
TI Multispecific and heterogeneous recognition of the gag protein by cytotoxic T lymphocytes (CTL) from HIV-infected patients: factors other than the MHC control the epitopic specificities.

L27 ANSWER 39 OF 101 MEDLINE on STN
TI HIV-specific CD8+ T-cell immune responses and viral replication.

L27 ANSWER 40 OF 101 MEDLINE on STN
TI Strain specificity of cell-mediated cytotoxic responses specific for the human immunodeficiency virus type 1 (HIV-1) envelope protein in seropositive donors: HIV-1Lai is more commonly recognized than HIV-1MN.

L27 ANSWER 41 OF 101 MEDLINE on STN
TI Membrane expression of HIV envelope glycoproteins triggers apoptosis in CD4 cells.

L27 ANSWER 42 OF 101 MEDLINE on STN
TI Detection of HIV-specific cell-mediated cytotoxicity in the peripheral blood from infected children.

L27 ANSWER 43 OF 101 MEDLINE on STN
TI Gag-specific cytotoxic T lymphocytes from human immunodeficiency virus type 1-infected individuals: Gag epitopes are clustered in three regions of the p24gag protein.

L27 ANSWER 44 OF 101 MEDLINE on STN
TI [The cellular immunity response to the gag protein of HIV-1].
La reponse immunitaire cellulaire contre la proteine gag de VIH-1.

L27 ANSWER 45 OF 101 MEDLINE on STN
TI Autoantibodies typical of non-organ-specific autoimmune diseases in HIV-seropositive patients.

L27 ANSWER 46 OF 101 MEDLINE on STN
TI The HIV Nef protein: facts and hypotheses.

L27 ANSWER 47 OF 101 MEDLINE on STN
TI Human immunodeficiency virus type 1 major neutralizing determinant exposed on hepatitis B surface antigen particles is highly immunogenic in primates.

L27 ANSWER 48 OF 101 MEDLINE on STN
TI The cytopathic effect of HIV is associated with apoptosis.

L27 ANSWER 49 OF 101 MEDLINE on STN
TI Processing of the precursor of NF-kappa B by the HIV-1 protease during acute infection.

L27 ANSWER 50 OF 101 MEDLINE on STN
TI Production of a non-functional nef protein in human immunodeficiency virus type 1-infected CEM cells.

=> d l27,ti,51-75

L27 ANSWER 51 OF 101 MEDLINE on STN
TI Primary cytotoxicity against the envelope glycoprotein of human immunodeficiency virus-1: evidence for antibody-dependent cellular cytotoxicity in vivo.

L27 ANSWER 52 OF 101 MEDLINE on STN
TI Mutational analysis of the HIV nef protein.

L27 ANSWER 53 OF 101 MEDLINE on STN
TI The cellular immune response to the human immunodeficiency virus.

L27 ANSWER 54 OF 101 MEDLINE on STN
TI T- and B-lymphocyte responses to human immunodeficiency virus (HIV) type 1 in macaques immunized with hybrid HIV/hepatitis B surface antigen particles.

L27 ANSWER 55 OF 101 MEDLINE on STN
TI Detection of primary cytotoxic T lymphocytes specific for the envelope glycoprotein of HIV-1 by deletion of the env amino-terminal signal sequence.

L27 ANSWER 56 OF 101 MEDLINE on STN
TI Effects of mutations in hyperconserved regions of the extracellular glycoprotein of human immunodeficiency virus type 1 on receptor binding.

L27 ANSWER 57 OF 101 MEDLINE on STN
TI Efficiency of poly(A).poly(U) as an adjuvant.

L27 ANSWER 58 OF 101 MEDLINE on STN
TI Multiple cytotoxic effector cells are induced by infection with the human

immunodeficiency virus.

L27 ANSWER 59 OF 101 MEDLINE on STN
TI Cell-mediated immune proliferative responses to HIV-1 of chimpanzees vaccinated with different vaccinia recombinant viruses.

L27 ANSWER 60 OF 101 MEDLINE on STN
TI Human immunodeficiency virus-specific cytotoxic responses of seropositive individuals: distinct types of effector cells mediate killing of targets expressing gag and env proteins.

L27 ANSWER 61 OF 101 MEDLINE on STN
TI Improved antigenicity of the HIV env protein by cleavage site removal.

L27 ANSWER 62 OF 101 MEDLINE on STN
TI Loss of CD4 membrane expression and CD4 mRNA during acute human immunodeficiency virus replication.

L27 ANSWER 63 OF 101 MEDLINE on STN
TI HIV F/3' orf encodes a phosphorylated GTP-binding protein resembling an oncogene product.

L27 ANSWER 64 OF 101 MEDLINE on STN
TI The effect of interferon treatment in rabies prophylaxis in immunocompetent, immunosuppressed, and immunodeficient mice.

L27 ANSWER 65 OF 101 MEDLINE on STN
TI Mapping arenavirus genes causing virulence.

L27 ANSWER 66 OF 101 MEDLINE on STN
TI Molecular characterization of the genomic S RNA segment from lymphocytic choriomeningitis virus.

L27 ANSWER 67 OF 101 MEDLINE on STN
TI Perturbation of differentiated functions in vivo during persistent viral infection. III. Decreased growth hormone mRNA.

L27 ANSWER 68 OF 101 MEDLINE on STN
TI Genetic reassortants of lymphocytic choriomeningitis virus: unexpected disease and mechanism of pathogenesis.

L27 ANSWER 69 OF 101 MEDLINE on STN
TI The use of lymphocytic choriomeningitis virus reassortants to map viral genes causing virulence.

L27 ANSWER 70 OF 101 MEDLINE on STN
TI Biology of cloned cytotoxic T lymphocytes specific for lymphocytic choriomeningitis virus. V. Recognition is restricted to gene products encoded by the viral S RNA segment.

L27 ANSWER 71 OF 101 MEDLINE on STN
TI Comparison of the effects of rabies virus infection and of combined interferon and poly(I).poly(C) treatment on the levels of 2',5'-adenyladenosine oligonucleotides in different organs of mice.

L27 ANSWER 72 OF 101 MEDLINE on STN
TI Perturbation of differentiated functions during viral infection in vivo. II. Viral reassortants map growth hormone defect to the S RNA of the lymphocytic choriomeningitis virus genome.

L27 ANSWER 73 OF 101 MEDLINE on STN
TI Genetic mapping of lymphocytic choriomeningitis virus pathogenicity: virulence in guinea pigs is associated with the L RNA segment.

L27 ANSWER 74 OF 101 MEDLINE on STN
TI Continuous production of interferon in normal mice: effect of

and interferon globulin, sex, age, strain and environment on the levels
of 2-5A synthetase and p67K kinase.

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L27  ANSWER 75 OF 101     MEDLINE on STN
TI   The S RNA segment of lymphocytic choriomeningitis virus codes for the
     nucleoprotein and glycoproteins 1 and 2.


=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20

=> e heard j m/au
E1           11     HEARD J K/AU
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E3          91 --> HEARD J M/AU
E4           2     HEARD J P/AU
E5           5     HEARD J S/AU
E6           7     HEARD J T JR/AU
E7           1     HEARD JAMIE/AU
E8           7     HEARD JEAN MICHEL/AU
E9           2     HEARD JEANNE/AU
E10          3     HEARD JEANNE K/AU
E11          2     HEARD JOY E/AU
E12         13     HEARD K/AU

=> s e8
L28           7 "HEARD JEAN MICHEL"/AU

=> s l28 not l20
L29           7 L28 NOT L20

=> d l29,ti,1-7

L29  ANSWER 1 OF 7     MEDLINE on STN
TI   Efficient reinnervation of hindlimb muscles by thoracic motor neurons
     after nerve cross-anastomosis in rats.

L29  ANSWER 2 OF 7     MEDLINE on STN
TI   Gene therapy for mucopolysaccharidosis.

L29  ANSWER 3 OF 7     MEDLINE on STN
TI   Mechanisms leading to sustained reversion of beta-thalassemia in mice by
     doxycycline-controlled Epo delivery from muscles.

L29  ANSWER 4 OF 7     MEDLINE on STN
TI   Lack of an immune response against the tetracycline-dependent
     transactivator correlates with long-term doxycycline-regulated transgene
     expression in nonhuman primates after intramuscular injection of
     recombinant adeno-associated virus.

L29  ANSWER 5 OF 7     MEDLINE on STN
TI   Pit2 assemblies at the cell surface are modulated by extracellular
     inorganic phosphate concentration.

L29  ANSWER 6 OF 7     MEDLINE on STN
TI   HIV-1 Nef-induced upregulation of DC-SIGN in dendritic cells promotes
     lymphocyte clustering and viral spread.

L29  ANSWER 7 OF 7     MEDLINE on STN
TI   Segregation of CD4 and CXCR4 into distinct lipid microdomains in T
     lymphocytes suggests a mechanism for membrane destabilization by human
     immunodeficiency virus.


=> file uspatful
COST IN U.S. DOLLARS                                 SINCE FILE     TOTAL
                                                          ENTRY   SESSION
FULL ESTIMATED COST                                       15.82     95.14

FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 29 Apr 2004 (20040429/PD)
FILE LAST UPDATED: 29 Apr 2004 (20040429/ED)
HIGHEST GRANTED PATENT NUMBER: US6728968
HIGHEST APPLICATION PUBLICATION NUMBER: US2004083524
CA INDEXING IS CURRENT THROUGH 29 Apr 2004 (20040429/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 29 Apr 2004 (20040429/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
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>>>  USPAT2 is now available.  USPATFULL contains full text of the      <<<
>>>  original, i.e., the earliest published granted patents or          <<<
>>>  applications.  USPAT2 contains full text of the latest US          <<<
>>>  publications, starting in 2001, for the inventions covered in      <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original      <<<
>>>  published document but also a list of any subsequent               <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention      <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL    <<<
>>>  records and may be searched in standard search fields, e.g., /PN,  <<<
>>>  /PK, etc.                                                          <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together         <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to           <<<
>>>  enter this cluster.                                                <<<
>>>                                                                     <<<
>>>  Use USPATALL when searching terms such as patent assignees,        <<<
>>>  classifications, or claims, that may potentially change from       <<<
>>>  the earliest to the latest publication.                           .<<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> e (DNA immun? or DNA injection or DNA-based immun? or DNA-based immun? or DNA-based vaccin? 
**** START OF FIELD ****
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                    D IMMUN? OR DNA-BASED VACCIN? OR GENE VACCIN?)/BI
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E5       278919     00/BI
E6            3     00-00-0/BI
E7            1     00-00-0D/BI
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E9            1     00-04-0/BI
E10           1     00-11-9/BI
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=> s (DNA immun? or DNA injection or DNA-based immun? or DNA-based vaccin? or gene vaccin?)
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          1484 DNA IMMUN?
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        104058 DNA
        402811 INJECTION
           974 DNA INJECTION
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        154009 IMMUN?
           134 DNA-BASED IMMUN?
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         36087 VACCIN?
           220 DNA-BASED VACCIN?
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         36087 VACCIN?
           145 GENE VACCIN?
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L30       2648 (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
               VACCIN? OR GENE VACCIN?)

=> s l30 and (CTL or cytotoxic T lymphocyte? or MHC class I or MHC class I-restricted)
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        937517 T
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       2159497 I
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       2159497 I
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           459 MHC CLASS I-RESTRICTED
                 (MHC(W)CLASS(W)I(W)RESTRICTED)
L31       1140 L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
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=> s l31 and exogenous
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L32        795 L31 AND EXOGENOUS

=> s l32 and (DNA immun?/clm or DNA injection/clm or DNA-based immun?/clm or DNA-based vaccin?/
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         65062 INJECTION/CLM
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             1 DNA-BASED IMMUN?/CLM
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        359341 BASED/CLM
          5460 VACCIN?/CLM
            12 DNA-BASED VACCIN?/CLM
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         22227 GENE/CLM
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         57190 PLASMID
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               /CLM OR DNA-BASED VACCIN?/CLM OR GENE VACCIN?/CLM OR PLASMID)

=> s l33 and plasmid/clm
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L34         77 L33 AND PLASMID/CLM

=> s l34 and py<2002
       3012123 PY<2002
L35         11 L34 AND PY<2002

=> s l34 and ay<2002
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L36         49 L34 AND AY<2002

=> d his

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L1            2 S E3

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     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
L28           7 S E8
L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002
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L36 ANSWER 1 OF 49 USPATFULL on STN
TI M cell directed vaccines

L36 ANSWER 2 OF 49 USPATFULL on STN
TI Molecular vaccine linking intercellular spreading protein to an antigen

L36 ANSWER 3 OF 49 USPATFULL on STN
TI Chimeric lyssavirus nucleic acids and polypeptides

L36 ANSWER 4 OF 49 USPATFULL on STN
TI Novel co-stimulatory molecules

L36 ANSWER 5 OF 49 USPATFULL on STN
TI ATTENUATED SALMONELLA STRAIN USED AS A VEHICLE FOR ORAL IMMUNIZATION

L36 ANSWER 6 OF 49 USPATFULL on STN
TI Nucleic acid and corresponding protein named 158P1H4 useful in the treatment and detection of bladder and other cancers

L36 ANSWER 7 OF 49 USPATFULL on STN
TI 103P2D6: tissue specific protein highly expressed in various cancers

L36 ANSWER 8 OF 49 USPATFULL on STN
TI Novel co-stimulatory molecules

L36 ANSWER 9 OF 49 USPATFULL on STN
TI Nucleic acids and corresponding proteins entitled 83P2H3 and CaTrF2E11 useful in treatment and detection of cancer

L36 ANSWER 10 OF 49 USPATFULL on STN
TI Compositions and methods for inducing activation of dendritic cells

L36 ANSWER 11 OF 49 USPATFULL on STN
TI Functional DNA clone for hepatitis C virus (HCV) and uses thereof

L36 ANSWER 12 OF 49 USPATFULL on STN
TI 55P4H4: gene expressed in various cancers

L36 ANSWER 13 OF 49 USPATFULL on STN
TI 125P5C8: a tissue specific protein highly expressed in various cancers

L36 ANSWER 14 OF 49 USPATFULL on STN
TI Methods and materials relataing to novel stem cell growth factor-like polypeptides and polynucleotides

L36 ANSWER 15 OF 49 USPATFULL on STN
TI Enhanced first generation adenovirus vaccines expressing codon optimized HIV1-Gag, Pol, Nef and modifications

L36 ANSWER 16 OF 49 USPATFULL on STN
TI 121P1F1: a tissue specific protein highly expressed in various cancers

L36 ANSWER 17 OF 49 USPATFULL on STN
TI Functional DNA clone for hepatitis C virus (HCV) and uses thereof

L36 ANSWER 18 OF 49 USPATFULL on STN
TI Vaccines using nucleic acid-lipid complexes

L36 ANSWER 19 OF 49 USPATFULL on STN
TI Nucleic acid and corresponding protein named 158P1D7 useful in the treatment and detection of bladder and other cancers

L36 ANSWER 20 OF 49 USPATFULL on STN
TI Methods for genetic immunization

L36 ANSWER 21 OF 49 USPATFULL on STN
TI BPC-1: a secreted brain-specific protein expressed and secreted by prostate and bladder cancer cells

L36 ANSWER 22 OF 49 USPATFULL on STN
TI Genetic immunization

L36 ANSWER 23 OF 49 USPATFULL on STN
TI 34P3D7: a tissue specific protein highly expressed in prostate cancer

L36 ANSWER 24 OF 49 USPATFULL on STN
TI Gene expression and delivery systems and uses

L36 ANSWER 25 OF 49 USPATFULL on STN
TI Introduction of naked DNA or RNA encoding non-human vertebrate peptide hormones or cytokines into a non-human vertebrate

L36 ANSWER 26 OF 49 USPATFULL on STN
TI IDENTIFICATION OF GENE SEQUENCES AND GENE PRODUCTS AND THEIR SPECIFIC FUNCTION AND RELATIONSHIP TO PATHOLOGIES IN A MAMMAL

L36 ANSWER 27 OF 49 USPATFULL on STN
TI FORMULATIONS FOR ELECTROPORATION

L36 ANSWER 28 OF 49 USPATFULL on STN
TI 83P5G4: a tissue specific protein highly expressed in prostate cancer

L36 ANSWER 29 OF 49 USPATFULL on STN
TI FUNCTIONAL DNA CLONE FOR HEPATITIS C VIRUS (HCV) AND USES THEREOF

L36 ANSWER 30 OF 49 USPATFULL on STN
TI Immunomodulatory polynucleotides in treatment of an infection by an intracellular pathogen

L36 ANSWER 31 OF 49 USPATFULL on STN
TI 98P7C3: homeodomain protein highly expressed in various cancers

L36 ANSWER 32 OF 49 USPATFULL on STN
TI Adenovirus carrying gag gene HIV vaccine

L36 ANSWER 33 OF 49 USPATFULL on STN
TI GTP-binding protein useful in treatment and detection of cancer

L36 ANSWER 34 OF 49 USPATFULL on STN
TI Delivery of polypeptide-encoding **plasmid** dna into the cytsol of macrophages by attenuated suicide bacteria

L36 ANSWER 35 OF 49 USPATFULL on STN
TI Formulations for electroporation

L36 ANSWER 36 OF 49 USPATFULL on STN
TI Compositions and methods for in vivo delivery of polynucleotide-based therapeutics

L36 ANSWER 37 OF 49 USPATFULL on STN
TI Method of inducing a **CTL** response

L36 ANSWER 38 OF 49 USPATFULL on STN
TI Eliciting HCV-specific antibodies

L36 ANSWER 39 OF 49 USPATFULL on STN
TI BPC-1: a secreted brain-specific protein expressed and secreted by prostate and bladder cancer cells

L36 ANSWER 40 OF 49 USPATFULL on STN

TI GENETIC VACCINE VECTOR ENGINEERING

L36 ANSWER 41 OF 49 USPATFULL on STN
TI Method of using mouse model for evaluation of HIV vaccines

L36 ANSWER 42 OF 49 USPATFULL on STN
TI Composite vaccine which contains antigen, antibody and recombinant DNA and its preparing method

L36 ANSWER 43 OF 49 USPATFULL on STN
TI Restenosis/atherosclerosis diagnosis, prophylaxis and therapy

L36 ANSWER 44 OF 49 USPATFULL on STN
TI Delivery of polypeptide-encoding **plasmid** DNA into the cytosol of macrophages by attenuated listeria suicide bacteria

L36 ANSWER 45 OF 49 USPATFULL on STN
TI Recombinant live feline immunodeficiency virus and proviral DNA vaccines

L36 ANSWER 46 OF 49 USPATFULL on STN
TI Compositions and methods for delivery of genetic material

L36 ANSWER 47 OF 49 USPATFULL on STN
TI DNA vaccination for induction of suppressive T cell response

L36 ANSWER 48 OF 49 USPATFULL on STN
TI Genetic immunization

L36 ANSWER 49 OF 49 USPATFULL on STN
TI Polynucleotide tuberculosis vaccine

=> d l36,cbib,ab,clm,10,22,24,25,36,37,47

L36 ANSWER 10 OF 49 USPATFULL on STN
2003:172706 Compositions and methods for inducing activation of dendritic cells
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Kabanov, Alexander V., Omaha, NE, UNITED STATES
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US 2003118550 A1 20030626
APPLICATION: US 2001-845938 A1 20010430 (9) <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions induce the activation of dendritic cells comprising a polynucleotide, such as viruses, RNA, DNA, **plasmid** DNA, or derivatives thereof and at least one block copolymer of alkylethers. The present invention further relates to compositions for inducing the activation of dendritic cells wherein the block copolymers are PLURONIC F127 and L61. More particular, the compositions comprise block copolymers PLURONIC F127/PLURONIC L61. The invention also relates to methods of inducing the activation of dendritic cells in animals comprising administering the compositions of the invention. Additionally, the present invention relates to methods of increasing the immune response of animals comprising administering the compositions of the present invention.

CLM What is claimed is:

1. Composition for inducing activation of dendritic cells comprising a polynucleotide, viral vector, or polynucleotide derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer.

2. The composition of claim 1 further comprising a polycation.

3. The composition of claim 2 wherein the polycation is a polyamine polymer.

4. The composition of claim 1 wherein the polycation is an oligoamine or an oligoamine conjugate.

5. The composition of claim 1 wherein there is a mixture of block copolymers.

6. The composition of claim 5 wherein the block copolymers comprise a mixture wherein at least one block copolymer with oxyethylene content of 50% or less, and at least one block copolymer with oxyethylene content of 50% or more.

7. The composition of claim 5 6 wherein the block copolymers comprise a mixture a first block copolymer component having an oxyethylene content of 50% or less, and a second block copolymer component having an oxyethylene content of 50% or more wherein the weight ratio of said second block copolymer to said first block copolymer is at least 2:1.

8. The composition of claim 6 wherein the block copolymers comprise a mixture a first block copolymer component having an oxyethylene content of 50% or less, and a second block copolymer component having an oxyethylene content of 50% or more wherein the weight ratio of said second block copolymer to said first block copolymer is at least 5:1.

9. The composition of claim 5 wherein the copolymers comprise a mixture wherein at least one block copolymer has an oxyethylene content of 70% or more and at least one block copolymer has an oxyethylene content of 50% or less.

10. The composition of claim 5 wherein N, according to the following expression, is from about 0.2 to about 9.0 and preferably from about 0.25 to about 1.5: ##EQU5## in which H_1 and H_2 are the number of oxypropylene units in the first and second block copolymers, respectively; L_1 is the number of oxyethylene units in the first block copolymer; L_2 is the number of oxyethylene units in the second block copolymer; m_1 is the weight proportion in the first block-copolymer; and m_2 is the weight proportion in the second block copolymer.

11. The composition of claim 5 wherein the mixture comprises the block copolymer PLURONIC® F127.

12. The composition of claim 1, wherein at least one of the block copolymers has the formula: ##STR15## in which x, y, z, i, and j have values from about 2 to about 400, and wherein for each R^1, R^2 pair, one is hydrogen and the other is a methyl group.

13. The composition of claim 1 wherein at least one of the block copolymers has the formula: ##STR16## in which x, y, z, i, and j have values from about 2 to about 400, and for each R^1, R^2 pair, one is hydrogen and the other is a methyl group.

14. The composition of claim 1 wherein the block copolymer comprises at least PLURONIC F127 and L61.

15. The composition of claim 14 wherein the ratio of PLURONIC F127:L61 is 8:1.

16. The composition of claim 14 wherein PLURONIC F127 is in the amount of about 2% w/v and PLURONIC L61 is in the amount of about 0.025% w/v.

17. The composition of claim 1 wherein said block copolymer is present in amounts insufficient for gel formation.

18. A composition for inducing the activation of dendritic cells comprising a polynucleotide or derivative thereof and at least one

polyoxyethylene-polyoxypropylene block copolymer, wherein the block copolymer is present at a concentration below about 15% wt/vol.

19. The composition of claim 18 wherein the block copolymer concentration is below about 10%.

20. The composition of claim 18 wherein the block copolymer concentration is below about 5%.

21. A composition for inducing the activation of dendritic cells comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer, wherein the composition forms a molecular solution or colloidal dispersion.

22. The composition of claim 21 wherein the colloidal dispersion is a suspension, emulsion, microemulsion, micelle, polymer complex, or other type of molecular aggregate.

23. The composition of claim 21 wherein the colloidal dispersion comprises molecular species that are less than about 300 nm.

24. The composition of claim 21 wherein the colloidal dispersion comprises molecular species that are less than about 100 nm.

25. The composition of claim 21 wherein the colloidal dispersion comprises molecular species that are less than about 50 nm.

26. The composition of claim 1 wherein the polynucleotide is RNA, DNA, **plasmid** DNA, virus, or viral vector.

27. The composition of claim 1 wherein the polynucleotide encodes a secreted or non-secreted protein, vaccine or antigen.

28. The composition of claim 1 comprising a gene expressing a secreted or non-secreted protein, vaccine or antigen and at least one gene expressing an adjuvant molecule operable to activate antigen presenting cells and induce immune response for enhanced antigen presentation.

29. A method of inducing activation of dendritic cells comprising administering a composition comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer.

30. The method of claim 30 wherein the block copolymers comprise at least PLURONIC F127 and L61.

31. The method of claim 30 wherein the block copolymer is present in amounts insufficient for gel formation.

32. A method of inducing activation of dentritic cells comprising administering a composition comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer, wherein the composition forms a molecular solution or colloidal dispersion.

33. The method of claim 32 wherein the block copolymers are PLURONIC F127 and L61.

34. A method of increasing the immune response of an animal comprising administering the composition according to claim 1.

35. The method of claim 34 wherein the block copolymers comprise at least PLURONIC F127 and L61.

36. The method of claim 34 wherein the composition is administered orally, topically, rectally, vaginally, parenterally, intramuscularly,

intradermally, subcutaneously, intraperitoneally, or intravenously.

37. A method of increasing the immune response of an animal comprising intramuscularly administering the composition according to claim 1.

38. The method of claim 37 wherein the block copolymers comprise at least PLURONIC F127 and L61.

39. The method of claim 37 wherein said composition is administered to at least one of smooth, skeletal, and cardiac muscles.

40. A method of increasing the immune response of an animal comprising intradermally administering the composition according to claim 1.

41. A compostion for inducing the activation of dentritic cells comprising at least one polyoxyethylene-polyoxypropylene block copolymer.

42. The composition of claim 41 further comprising a polycation.

43. The composition of claim 42 wherein the polycation is a polyamine polymer.

44. The composition of claim 41 wherein the polycation is an oligoamine or an oligoamine conjugate.

45. The composition of claim 41 wherein there is a mixture of block copolymers.

46. The composition of claim 45 wherein the block copolymers comprise a mixture wherein at least one block copolymer with oxyethylene content of 50% or less, and at least one block copolymer with oxyethylene content of 50% or more.

47. The composition of claim 46 wherein the ratio by weight of the block copolymer with oxyethylene content of 50% or less to the block copolymer with oxyethylene content of 50% or more is 1:2.

48. The composition of claim 46 wherein the ratio by weight of the block copolymer with oxyethylene content of 50% or less to the block copolymer with oxyethylene content of 50% or more is 1:5.

49. The composition of claim 45 wherein the copolymers comprise a mixture wherein at least one block copolymere with oxyethylene content of 70% or more and at least one block copolymer with oxyethylene content of 50% or less.

50. The composition of claim 45 wherein N, according to the following expression, is from about 0.2 to about 9.0 and preferably from about 0.25 to about 1.5: ##EQU6## in which H_1 and H_2 are the number of oxypropylene units in the first and second block copolymers, respectively; L_1 is the number of oxyethylene units in the first block copolymer; L_2 is the number of oxyethylene units in the second block copolymer; m_1 is the weight proportion in the first block-copolymer; and m_2 is the weight proportion in the second block copolymer.

51. The composition of claim 45 wherein the mixture comprises the block copolymer PLURONIC® F127.

52. The composition of claim 41, wherein at least one of the block copolymers has the formula: ##STR17## in which x, y, z, i, and j have values from about 2 to about 400, and wherein for each R^1, R^2 pair, one is hydrogen and the other is a methyl group.

53. The composition of claim 41 wherein at least one of the block copolymers has the formula: ##STR18## in which x, y, z, i, and j have values from about 2 to about 400, and for each R^1, R^2 pair, one is hydrogen and the other is a methyl group.

54. The composition of claim 41 wherein the block copolymer comprises at least PLURONIC F127 and L61.

55. The composition of claim 40 wherein the block copolymer is present in amounts insufficient for gel formation.

56. A composition for inducing the activation of dendritic cells comprising at least one polyoxyethylene-polyoxypropylene block copolymer, wherein the composition forms a molecular solution or colloidal dispersion.

57. The composition of claim 56 wherein the colloidal dispersion is a suspension, emulsion, microemulsion, micelle, polymer complex, or other type of molecular aggregate.

58. The composition of claim 56 wherein the colloidal dispersion comprises molecular species that are less than about 300 nm.

59. The composition of claim 56 wherein the colloidal dispersion comprises molecular species that are less than about 100 nm.

60. The composition of claim 56 wherein the colloidal dispersion comprises molecular species that are less than about 50 nm.

61. A composition for inducing activation of dendritic cells comprising a polynucleotide or derivative thereof and at least one polycationic polymer having a plurality of cationic repeating units.

62. A polynucleotide composition according to claim 61 wherein said polycationic polymer is a cationic homopolymer, copolymer or block copolymer comprising one or more of the following fragments: (a) at least one aminoalkylene monomer selected from a group consisting of: (i) a tertiary amine monomer of the formula ##STR19## and, (ii) a secondary amine monomer of the formula ##STR20## in which: each of R^1, R^4, R^5, R^6 and R^8 taken independently of each other is hydrogen, alkyl of 2 to 8 carbon atoms, another A monomer, or another B monomer; each of R^2, R^3 and R^7, taken independently of each other, is a straight or branched alkanediyl of the formula --(C_{zH2z})-- wherein z has a value of from 2 to 8; (b) cationic amino acids; (c) (--OPO(NH--R^{9}--$NR^{10R11R12}$)O--R^{8}--) in which R^9 is a stright chain aliphatic group of from 1-12 carbon atoms and R^8 is --$(CH_2)_{n--CH}$(R^{13})--where n is an integer from 0 to 5, R^{10}, R^{11} and R^{12} are independently hydrogen or alkyl of 1 to 4 carbon atoms and R^{13} is a hydrogen, cycloalkyl having 3-8 carbon atoms, or alkyl of 1-2 carbon atoms; and (d) vinylpyridine or a derivative thereof.

63. A composition according to claim 62 comprising a polynucleotide and a polymer of a plurality of segments, wherein the polymers comprise at least one polycationic segment which is cationic homopolymer, copolymer, or block copolymer, or quaternary salt thereof; and either, (a) at least one straight or branched chain polyether segment of from 5 to about 400 monomer units which polyether segment is: (i) a homopolymer of at least one alkyleneoxy monomer --$OC_{nH2n--in}$ which n has a value from 2 to 3; or, (ii) a copolymer or block copolymer of said first alkyleneoxy monomer and a second different alkyleneoxy monomer --OC_{mH2m--}, in which n has a value from 2 to 3 and m has a value from 2 to 4 or, (b) a homopolymer or copolymer of at least one monomer from a group consisting of acrylamide, glycerol, vinyl alcohol,

vinyl pyrrolidine, vinylpyridine N-oxide, oxazoline, morpholino acrylamide, and derivatives thereof.

64. A composition according to claim 63 wherein said first alkyleneoxy monomer is ethyleneoxy ($--OCH_{2CH2--}$) and said second alkyleneoxy monomer is propyleneoxy ($--OCH(CH_3)CH_{2--}$).

65. A composition of claim 63 wherein the polycationic polymer, at physiological pH, comprise at least six cationic groups.

66. A polynucleotide composition according to claim 63 wherein the polycationic polymer, at physiological pH, contain a plurality of cationic groups separated by about 3 Å to about 12 Å.

67. A polynucleotide composition according to claim 63 wherein each of said polyether segments has from about 5 to about 80 monomeric units and said polycationic segment is a homopolymer, copolymer or block copolymer of from 2 to about 180 of the same or different monomeric units of the formula $--NH--R^{\circ}--$ in which R_o is a straight chain aliphatic group of 2 to 6 carbon atoms which may be optionally substituted.

68. A composition according to claim 69 wherein the polycationic polymer is covalently linked with at least one nonionic polymer segment.

69. A method of inducing activation of dendritic cells comprising administering a composition comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer.

70. A method of inducing the activation of dendritic cells comprising administering a composition comprising at least one polyoxyethylene-polyoxypropylene block copolymer, wherein the block copolymer is present in amounts insufficient for gel formation.

71. The method of claim 70 wherein the block copolymers comprise at least PLURONIC F127 and L61.

72. A method of inducing activation of dentritic cells comprising administering a composition comprising at least one polyoxyethylene-polyoxypropylene block copolymer, wherein the composition forms a molecular solution or colloidal dispersion.

73. The method of claim 72 wherein the block copolymers are PLURONIC F127 and L61.

74. A method of increasing the immune response of an animal comprising administering the composition according to claim 72.

75. The method of claim 72 wherein the composition is administered orally, topically, rectally, vaginally, parenterally, intramuscularly, intradermally, subcutaneously, intraparitoneally, or intravenously.

76. The method of claim 72 wherein said composition is administered to at least one of smooth, skeletal, and cardiac muscles.

77. A method of improving the immune response of an animal comprising intradermally administering the composition according to claim 34.

L36 ANSWER 22 OF 49 USPATFULL on STN
2002:276069 Genetic immunization.

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Williams, William V., Havertown, PA, United States
Wang, Bin, Havertown, PA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)The Wistar Institute, Philadelphia, PA, United

States (U.S. Corporation)
US 6468982 B1 20021022
APPLICATION: US 1997-880576 19970623 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods of prophylactic and therapeutic immunization of an individual against pathogen infection, diseases associated with hyperproliferative cells and autoimmune diseases are disclosed. The methods comprise the steps of administering to cells of an individual, a nucleic acid molecule that comprises a nucleotide sequence that encodes a protein which comprises at least one epitope that is identical or substantially similar to an epitope of a pathogen antigen, a hyperproliferative cell associated protein or a protein associated with autoimmune disease respectively. In each case, nucleotide sequence is operably linked to regulatory sequences to enable expression in the cells. The nucleic acid molecule is free of viral particles and capable of being, expressed in said cells. The cells may be contacted cells with a cell stimulating agent. Methods of prophylactically and therapeutically immunizing an individual against HIV are disclosed. Pharmaceutical compositions and kits for practicing methods of the present invention are disclosed.

CLM What is claimed is:

1. A method for inducing an immune response in an individual against an antigen comprising orally administering to said individual, a pharmaceutical composition comprising bupivacaine and DNA molecules that comprise a DNA sequence that encodes said antigen, said DNA sequence operatively linked to regulatory sequences which control the expression of said DNA sequence; wherein said DNA molecules are free from viral particles and when said DNA molecules are taken up by cells of said individual, said DNA sequence is expressed in said cells and an immune response is generated against said antigen.

2. The method of claim 1 wherein said DNA molecules are plasmids.

3. The method of claim 1 wherein said pharmaceutical composition consists essentially of DNA molecules and bupivacaine.

4. The method of claim 1 wherein said immune response generated against said antigen is an immune response against a pathogen antigen.

5. The method of claim 4 wherein said pathogen is an intracellular pathogen.

6. A method of immunizing an individual against a Herpes simplex 2 virus (HSV2) antigen comprising orally administering to said individual, a pharmaceutical composition comprising bupivacaine and DNA molecules that comprise a DNA sequence that encodes said antigen, said DNA sequence operatively linked to regulatory sequences which control the expression of said DNA sequence; wherein said DNA molecules are free of viral particles and when said DNA molecules are taken up by cells of said individual, said DNA sequence is expressed in said cells and a protective immune response is generated against said antigen.

7. A method of inducing an immune response in an individual against a pathogen comprising orally administering to said individual, a pharmaceutical composition comprising bupivacaine and DNA molecules that comprise a DNA sequence that encodes an antigen from said pathogen, said DNA sequence operatively linked to regulatory sequences which control the expression of said DNA sequence; wherein said DNA molecules are free of viral particles and when said DNA molecules are taken up by cells of said individual, said DNA sequence is expressed in said cells and an immune response is generated against said antigen.

8. The method of claim 7 wherein said DNA molecules are plasmids.

9. The method of claim 7 wherein said pharmaceutical composition consists essentially of DNA molecules and bupivacaine.

10. The method of claim 7 wherein said pathogen is an intracellular pathogen.

11. The method of claim 7 wherein said pathogen is a virus.

12. A method of immunizing an individual against a Herpes simplex 2 virus (HSV2) comprising orally administering to said individual, a pharmaceutical composition comprising bupivacaine and DNA molecules that comprise a DNA sequence that encodes an antigen from said pathogen, said DNA sequence operatively linked to regulatory sequences which control the expression of said DNA sequence; wherein said DNA molecules are free of viral particles and when said DNA molecules are taken up by cells of said individual, said DNA sequence is expressed in said cells and a protective immune response is generated against said antigen.

13. A method of treating an individual who is infected by Herpes simplex 2 virus (HSV2) comprising orally administering to said individual, a pharmaceutical composition comprising bupivacaine and DNA molecules that comprise a DNA sequence that encodes an antigen from HSV2, said DNA sequence operatively linked to regulatory sequences which control the expression of said DNA sequence; wherein said DNA molecules are free from viral particles and when said DNA molecules are taken up by cells of said individual, said DNA sequence is expressed in said cells and a therapeutically effective immune response is generated.

14. The method of claim 13 wherein said DNA molecule is a **plasmid**.

15. The method of claim 13 wherein said pharmaceutical composition consists essentially of DNA molecules and bupivacaine.

L36 ANSWER 24 OF 49 USPATFULL on STN
2002:221798 Gene expression and delivery systems and uses.
Nordstrom, Jeff, College Station, TX, UNITED STATES
Freimark, Bruce, Spring, TX, UNITED STATES
Deshpande, Deepa, The Woodlands, TX, UNITED STATES
US 2002119940 A1 20020829
APPLICATION: US 2001-754014 A1 20010103 (9) <--
PRIORITY: WO 1997-US18832 19971010
US 1996-28687P 19961018 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Plasmid** expression systems for delivery of DNA coding sequences to a mammal are described which provide expression of multiple coding sequences from a single **plasmid**. Also described are particular lipid/DNA delivery systems having advantageous characteristics of size, charge ratio, and proportion of supercoiled DNA, and methods of preparing and using such delivery systems for treatment or as immunization adjuvants.

CLM What is claimed is:
1. A **plasmid** for expression of recombinant eucaryotic genes comprising: a first transcription unit comprising a first transcriptional control sequence transcriptionally linked with a first 5'-untranslated region, a first synthetic intron, a first coding sequence, and a first synthetic 3'-untranslated region/poly(A) signal, wherein said first synthetic intron is between said control sequence and said first coding sequence; and a second transcription unit comprising a second transcriptional control sequence transcriptionally linked with a second 5'-untranslated region, a second synthetic intron, a second coding sequence, and a second synthetic 3'-untranslated region/poly(A) signal, wherein said second synthetic intron is between said control sequence and said second coding sequence.

2. The **plasmid** of claim 1, wherein said first transcriptional control sequence or said second transcriptional control sequence comprise

cytomegalovirus promoter/enhancer sequences.

3. The **plasmid** of claim 1, wherein said first coding sequence or said second coding sequence encode a therapeutic molecule or a subunit of a therapeutic molecule.

4. The **plasmid** of claim 1, wherein said first and second transcriptional control sequences are the same.

5. The **plasmid** of claim 1, wherein said first and second transcriptional control sequences are different.

6. The **plasmid** of claim 1, wherein said first coding sequence and said second coding sequence comprise a sequence coding for the p40 subunit of human IL-12 and a sequence coding for the p35 subunit of human IL-12.

7. The **plasmid** of claim 6, wherein said sequence coding for the p40 subunit of human IL-12 is 5' to said sequence coding for the p35 subunit of human IL-12.

8. A **plasmid** for expression of recombinant eucaryotic genes, comprising an intron having variable splicing, a first coding sequence, and a second coding sequence.

9. The **plasmid** of claim 8, further comprising: a transcriptional control sequence transcriptionally linked with a first coding sequence and a second coding sequence; a 5'-untranslated region; an intron 5' to said first coding sequence; an alternative splice site 3' to said first coding sequence and 5' to said second coding sequence; and a 3'-untranslated region/poly(A) signal.

10. The **plasmid** of claim 9, wherein said first coding sequence or said second coding sequence encode a therapeutic molecule or a subunit of a therapeutic molecule.

11. The **plasmid** of claim 9, wherein said transcriptional control sequence comprises a cytomegalovirus promoter/enhancer sequence.

12. The **plasmid** of claim 8, wherein said first coding sequence and said second coding sequence comprise a sequence coding for the p40 subunit of human IL-12 and a sequence coding for the p35 subunit of human IL-12.

13. A **plasmid** for expression of recombinant eucaryotic genes comprising: a transcriptional control sequence transcriptionally linked with a first coding sequence, an IRES sequence, a second coding sequence, and a 3'-untranslated region/poly(A) signal, wherein said IRES sequence is between said first coding sequence and said second coding sequence; and an intron between said promoter and said first coding sequence.

14. The **plasmid** of claim 13, wherein said transcriptional control sequence comprises a cytomegalovirus promoter/enhancer sequence.

15. The **plasmid** of claim 13, wherein said first coding sequence and said second coding sequence comprise a sequence coding for the p40 subunit of human IL-12 and a sequence coding for the p35 subunit of human IL-12.

16. The **plasmid** of claim 13, wherein said IRES sequence is from an encephalomyocarditis virus.

17. A DNA sequence coding for human IL-12 subunit, comprising a synthetic nucleotide sequence having less than 50% identity to a natural human IL-12 subunit coding sequence.

18. The DNA sequence of claim 17, wherein said synthetic nucleotide sequence comprises a sequence having at least 99% sequence identity to the sequence of SEQ ID NO. 3.

19. The DNA sequence of claim 18, wherein said synthetic nucleotide sequence comprises a nucleotide sequence identical to the sequence of SEQ ID NO. 3 or 4.

20. The DNA sequence of claim 17, wherein said synthetic nucleotide sequence comprises a sequence having at least 99% sequence identity to the sequence of SEQ ID NO. 7.

21. The DNA sequence of claim 20, wherein said synthetic nucleotide sequence comprises a nucleotide sequence identical to the sequence of SEQ ID NO. 7 or 8.

22. A composition for delivery of a DNA molecule in a mammal, comprising a cationic lipid with a neutral co-lipid, prepared as a liposome having an extrusion size of about 800 nanometers; and a quantity of DNA comprising a coding sequence.

23. The composition of claim 22, wherein said DNA is at least about 80% supercoiled.

24. The composition of claim 23, wherein said DNA is at least about 90% supercoiled.

25. The composition of claim 24, wherein said DNA is at least about 95% supercoiled.

26. The composition of claim 22, wherein said cationic lipid and said DNA are present in a negative to positive charge ratio of about 1:3.

27. The composition of claim 22, further comprising an isotonic carbohydrate solution.

28. The composition of claim 27, wherein said isotonic carbohydrate solution consists essentially of about 10% lactose.

29. A composition of claim 22, wherein said cationic lipid is DOTMA and said neutral co-lipid is cholesterol.

30. A composition for delivery of a DNA molecule in a mammal, comprising a cationic lipid with a neutral co-lipid; and a quantity of DNA comprising a coding sequence, wherein said cationic lipid and said DNA are present in a negative to positive charge ratio of about 1:3.

31. The composition of claim 30, wherein said DNA is at least about 80% supercoiled.

32. The composition of claim 31, wherein said DNA is at least about 90% supercoiled.

33. The composition of claim 32, wherein said DNA is at least about 95% supercoiled.

34. The composition of claim 30, further comprising an isotonic carbohydrate solution.

35. The composition of claim 34, wherein said isotonic carbohydrate solution consists essentially of about 10% lactose.

36. A composition of claim 30, wherein said cationic lipid is DOTMA and said neutral co-lipid is cholesterol.

37. A method for preparing a composition for delivery of a DNA to a

mammal, comprising the steps of: a. preparing a DNA comprising a coding sequence; b. preparing liposomes having an extrusion size of about 800 nm, wherein said liposomes comprise a cationic lipid and a neutral co-lipid; and c. combining said liposomes with said DNA in amounts such that said cationic lipid and said DNA are present in a negative to positive charge ratio of about 1:3.

38. A method of treatment of a mammalian condition or disease, comprising administering to a mammal suffering from said condition or disease an amount of a composition for delivery of a DNA molecule in a mammal, wherein said DNA comprises a coding sequence encoding a therapeutic molecule or a subunit thereof, and wherein said composition comprises a cationic lipid, a neutral co-lipid, and said DNA, and has a negative to positive charge ratio of about 1:3 for said cationic lipid and said DNA.

39. The method of claim 38, wherein said composition is prepared for administration by ultrasonic nebulization.

40. The method of claim 38, wherein said DNA comprises two coding sequences which encode human IL-12 p40 and p35 subunits.

41. The method of claim 38, wherein said disease or condition is asthma.

42. The method of claim 38, wherein said disease or condition is a cancer.

43. A vaccine adjuvant comprising a cationic lipid, a neutral co-lipid, and DNA, wherein said DNA comprises a sequence encoding the p40 subunit of IL-12 and the p35 subunit of IL-12, and wherein said cationic lipid and said DNA are present in a negative to positive charge ratio of about 1:3.

44. A method of enhancing the response of a mammal to a vaccine, comprising the step of administering to said mammal a vaccine and an adjuvant, wherein said adjuvant comprises a cationic lipid, a neutral co-lipid, and DNA, said DNA comprising a sequence encoding the p40 subunit of IL-12 and the p35 subunit of IL-12, and wherein said cationic lipid and said DNA are present in a negative to positive charge ratio of about 1:3.

L36 ANSWER 25 OF 49 USPATFULL on STN
2002:206626 Introduction of naked DNA or RNA encoding non-human vertebrate peptide hormones or cytokines into a non-human vertebrate.
Martin, Stephen, Portage, MI, UNITED STATES
Russell, Paul F., Portage, MI, UNITED STATES
US 2002111323 A1 20020815
APPLICATION: US 2001-898428 A1 20010702 (9) <--
PRIORITY: US 1998-84418P 19980506 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the introduction of naked DNA or RNA molecules encoding non-human vertebrate peptide hormones or cytokines into a non-human vertebrate to achieve delivery of the non-human vertebrate peptide hormone or cytokine. The invention thus provides an alternative to directly administering the polypeptide of interest.

CLM What is claimed is:
1. A method for delivering a desired physiologically active protein, polypeptide or peptide growth hormone or cytokine to a non-human vertebrate, comprising injecting into the muscle of said vertebrate a non-infectious, non-immunogenic, non-integrating DNA sequence encoding said growth hormone or cytokine operably linked to a promoter, wherein said DNA sequence is free from association with transfection-facilitating proteins, viral particles, liposomal formulations, charged lipids and calcium phosphate precipitating agents, whereby said DNA

sequence is expressed and induces an increase in body weight gain in said vertebrate.

2. The method of claim 1 wherein said vertebrate is a mammal.

3. The method of claim 1 wherein said growth hormone or cytokine is selected from the group consisting of porcine growth hormone, bovine growth hormone, canine growth hormone, bovine IGF-1, porcine IGF-1, canine IGF-1, bovine growth hormone releasing factor, porcine growth hormone releasing factor, and canine growth hormone releasing factor.

4. The method of claim 3, wherein said growth hormone or cytokine has an amino acid sequence identical to the native growth hormone or cytokine of said vertebrate.

5. The method of claim 4, wherein said growth hormone or cytokine is porcine growth hormone, and said vertebrate is a pig.

6. The method of claim 4, wherein said growth hormone or cytokine is bovine growth hormone, and said vertebrate is a cow.

7. The method of claim 4, wherein said growth hormone or cytokine is canine growth hormone, and said vertebrate is a dog.

8. The method of claim 4, wherein said growth hormone or cytokine is bovine IGF-1, and said vertebrate is a cow.

9. The method of claim 4, wherein said growth hormone or cytokine is porcine IGF-1, and said vertebrate is a pig.

10. The method of claim 4, wherein said growth hormone or cytokine is canine IGF-1, and said vertebrate is a dog.

11. The method of claim 4, wherein said growth hormone or cytokine is bovine growth hormone releasing factor, and said vertebrate is a cow.

12. The method of claim 4, wherein said growth hormone or cytokine is porcine growth hormone releasing factor, and said vertebrate is a pig.

13. The method of claim 4, wherein said growth hormone or cytokine is canine growth hormone releasing factor, and said vertebrate is a dog.

14. The method of claim 1, wherein said DNA is free from a delivery vehicle to facilitate entry of the DNA into the cell.

15. The method of claim 1, wherein said DNA comprises a **plasmid**.

16. The method of claim 1, wherein said promoter is a cell specific or tissue specific promoter.

17. The method of claim 1, wherein said muscle is skeletal muscle.

18. The method of claim 1, wherein said injection comprises impressing said DNA through the skin.

19. The method of claim 1, wherein said injection comprises injection of said DNA through a needle.

20. The method of claim 1, wherein said injection comprises injecting said DNA into the interstitial space of said muscle resulting in transfection of said DNA into muscle cells of said vertebrate.

21. The method of claim 1, wherein said DNA is operably linked to a DNA sequence encoding a signal peptide wherein the signal peptide directs the secretion of the growth hormone or cytokine.

22. The method of claim 1, where the expression of said growth hormone or cytokine is transitory.

23. The method of claim 1, wherein said growth hormone or cytokine is produced for at least one month.

L36 ANSWER 36 OF 49 USPATFULL on STN
2002:32536 Compositions and methods for in vivo delivery of polynucleotide-based therapeutics.
Manthorpe, Marston, San Diego, CA, UNITED STATES
Hartikka, Jukka, San Diego, CA, UNITED STATES
Sukhu, Loretta, San Diego, CA, UNITED STATES
Vical Incorporated, San Diego, CA (U.S. corporation)
US 2002019358 A1 20020214
APPLICATION: US 2001-839574 A1 20010423 (9) <--
PRIORITY: US 2000-198823P 20000421 (60)
US 2000-253153P 20001128 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to pharmaceutical compositions and methods to improve expression of **exogenous** polypeptides into vertebrate cells in vivo, utilizing delivery of polynucleotides encoding such polypeptides. More particularly, the present invention provides the use of salts, in particular sodium and potassium salts of phosphate, in aqueous solution, and auxiliary agents, in particular detergents and surfactants, in pharmaceutical compositions and methods useful for direct polynucleotide-based polypeptide delivery into the cells of vertebrates.

CLM What is claimed is:

1. A composition comprising: (a) about 1 ng to about 30 mg of a polynucleotide in aqueous solution which operably encodes a polypeptide upon delivery to vertebrate cells in vivo; (b) a salt selected from the group consisting of sodium acetate, sodium bicarbonate, sodium sulfate, potassium phosphate, potassium acetate, potassium bicarbonate, potassium sulfate, sodium glycero-phosphate, sodium glucose-6-phosphate, and reaction, association, or dissociation products thereof; wherein said salt is dissolved in said aqueous solution at a molar concentration ranging from about 20 mM to about 300 mM.

2. The composition of claim 1, wherein said salt is sodium acetate or reaction, association, or dissociation products thereof.

3. The composition of claim 1, wherein said salt is sodium bicarbonate or reaction, association, or dissociation products thereof.

4. The composition of claim 1, wherein said salt is sodium sulfate or reaction, association, or dissociation products thereof.

5. The composition of claim 1, wherein said salt is sodium acetate or reaction, association, or dissociation products thereof.

6. The composition of claim 1, wherein said salt is potassium phosphate or reaction, association, or dissociation products thereof.

7. The composition of claim 1, wherein said salt is potassium acetate or reaction, association, or dissociation products thereof.

8. The composition of claim 1, wherein said salt is potassium bicarbonate or reaction, association, or dissociation products thereof.

9. The composition of claim 1, wherein said salt is potassium sulfate or reaction, association, or dissociation products thereof.

10. The composition of claim 1, wherein said salt is sodium glycero-phosphate or reaction, association, or dissociation products

thereof.

11. The composition of claim 1, wherein said salt is sodium glucose-6-phosphate or reaction, association, or dissociation products thereof.

12. The composition of claim 1, wherein said salt is present at a molar concentration of about 100 mM to about 200 mM.

13. The composition of claim 1, wherein said salt is present at a molar concentration of about 150 mM.

14. The composition of claim 12, further comprising chloride ion in said aqueous solution at a molar equivalent concentration of zero (0) mM to about 125 mM, and reaction, association, or dissociation products thereof.

15. The composition of claim 14, comprising chloride ion at a molar equivalent concentration from 0 mM to about 10 mM.

16. The composition of claim 15, which is substantially free of chloride ion.

17. The composition of claim 1, wherein said polynucleotide is DNA operably associated with a promoter.

18. The composition of claim 17, wherein said polynucleotide is contained in a **plasmid**.

19. The composition of claim 1, wherein said polynucleotide is RNA.

20. The composition of claim 19, wherein said polynucleotide is contained in messenger RNA.

21. The composition of claim 1, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

22. The composition of 21, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, Leishmania elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, analogs, or derivatives thereof.

23. The composition of claim 21, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and antigenic fragments, derivatives, or analogs thereof.

24. The composition of claim 21, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and immunogenic fragments,

derivatives, or analogs thereof.

25. The composition of claim 21, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a chemokine, and fragments, derivatives, or analogs thereof having immunomodulatory activity.

26. The composition of claim 21, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs, or derivatives thereof.

27. The composition of claim 1, further comprising a transfection facilitating agent selected from the group consisting of calcium phosphate, gold, tungsten, or other metal particles, peptides, proteins, and polymers.

28. The composition of claim 1, further comprising an auxiliary agent selected from the group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, and a condensing agent.

29. The composition of claim 28, wherein said auxiliary agent selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic® L44, Pluronic® L61, Pluronic® L62, Pluronic® L64, Pluronic® L81, Pluronic® L92, Pluronic® L101, Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet® P40, Tween-20®, Tween-80®, Triton X-100.TM., Triton X-114.TM., Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

30. The composition of claim 29, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100.TM., Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

31. The composition of claim 30, wherein said auxiliary agent is Pluronic® R 25R2.

32. The composition of claim 30, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100.TM.; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to

1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

33. The composition of claim 32, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

34. The composition of claim 32, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100.TM.; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64; about 0.001% (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

35. The composition of claim 32, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

36. The composition of claim 32, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01% (v/v) Triton X-100.TM.; 4% Pluronic® F68; 1.0% (w/v) Pluronic® F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

37. The composition of claim 33, comprising 0.01% (w/v) of Pluronic® R 25R2.

38. A method for delivering a polypeptide to a vertebrate, comprising administering into a tissue or cavity of said vertebrate the composition of claim 1; wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

39. The method of claim 38; wherein said polypeptide is a therapeutic polypeptide; wherein said vertebrate is in need of the therapy provided by said polypeptide; and wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

40. The method of claim 38, wherein said polypeptide is an immunogenic or immunomodulatory polypeptide; wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

41. The method of claim 38, wherein said polypeptide is a functional self polypeptide; wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and wherein said functional self polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

42. The method of claim 38, wherein said vertebrate is a mammal.

43. The method of claim 42, wherein said mammal is a human.

44. The method of claim 38, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue, intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

45. The method of claim 38, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

46. The method of claim 33, wherein said cavity comprises a mucosal surface.

47. The method of claim 45, wherein said tissue is muscle.

48. The method of claim 47, wherein said tissue is skeletal muscle, smooth muscle, or myocardium.

49. The method of claim 38, wherein said administration is intravenous.

50. The method of claim 38, wherein said administration is by a route selected from the group consisting of intramuscular, intratracheal, intranasal, transdermal, interdermal, subcutaneous, intraocular, vaginal, rectal, intraperitoneal, intraintestinal and inhalation.

51. The method of claim 38, wherein said administration route is intramuscular.

52. The method of claim 51, wherein said administration is by intramuscular injection.

53. A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 1.

54. A pharmaceutical kit comprising: (a) a container holding about 1 ng to about 30 mg of a polynucleotide which operably encodes a polypeptide within vertebrate cells in vivo; and (b) an amount of a salt selected from the group consisting of sodium acetate, sodium bicarbonate, sodium sulfate, potassium phosphate, potassium acetate, potassium bicarbonate, potassium sulfate, sodium glycero-phosphate and sodium glucose-6-phosphate, wherein said salt, when dissolved in an prescribed volume of distilled water, results in an aqueous solution with a molar concentration of said salt from about 20 mM to about 300 mM, or reaction, association, or dissociation products thereof; whereby said polynucleotide is provided in a prophylactically or therapeutically effective amount to treat a vertebrate.

55. The pharmaceutical kit of claim 54, wherein (b) is in the container of (a).

56. The pharmaceutical kit of claim 54, wherein (b) is in a separate container from (a).

57. The pharmaceutical kit of claim 54, further comprising an administration means.

58. A composition comprising: (a) about 1 ng to about 30 mg of a polynucleotide which operably encodes a polypeptide upon delivery to vertebrate cells in vivo; (b) an auxiliary agent selected from the

group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, a condensing agent, combinations thereof, and reaction, association and dissociation products thereof; and (c) water.

59. The composition of claim 58, wherein said auxiliary agent is selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic® L44, Pluronic® L61, Pluronic® L62, Pluronic® L64, Pluronic® L81, Pluronic® L92, Pluronic® L101, Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet® P40, Tween-20®, Tween-80®, Triton X-100.TM., Triton X-114.TM., Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

60. The composition of claim 59, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100.TM., Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

61. The composition of claim 60, wherein said auxiliary agent is Pluronic® R 25R2.

62. The composition of claim 60, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100.TM.; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 17R4; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

63. The composition of claim 62, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

64. The composition of claim 62, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100.TM.; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64; about 0.001% (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

65. The composition of claim 64, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

66. The composition of claim 64, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01%

F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

67. The composition of claim 66, comprising 0.01% (w/v) of Pluronic® R 25R2.

68. The composition of claim 58, further comprising a salt M-X wherein M is a cation selected from the group consisting of sodium and potassium, and wherein X is an anion selected from the group consisting of phosphate, acetate, bicarbonate, sulfate, and pyruvate.

69. The composition of claim 68, wherein said salt is sodium phosphate or potassium phosphate.

70. The composition of claim 58, wherein said polynucleotide is DNA operably associated with a promoter.

71. The composition of claim 70, wherein said polynucleotide is contained on a **plasmid**.

72. The composition of claim 58, wherein said polynucleotide is RNA.

73. The composition of claim 72, wherein said polynucleotide is contained in messenger RNA.

74. The composition of claim 58, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

75. The composition of claim 74, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, Leishmania elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, analogs, or derivatives thereof.

76. The composition of claim 74, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergen, a tumor specific polypeptide and antigenic fragments, analogs, or derivatives thereof.

77. The composition of claim 74, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergen, a tumor specific polypeptide, and immunogenic fragments, analogs, or derivatives thereof.

78. The composition of claim 74, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a

chemokine, and immunomodulatory fragments, analogs, or derivatives thereof.

79. The composition of claim 74, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs,and derivatives thereof.

80. The composition of claim 58, further comprising a transfection facilitating agent selected from the group consisting of cationic lipids, calcium phosphate, alum, gold, tungsten, or other metal particles, peptides, proteins, and polymers.

81. The composition of claim 80, wherein said transfection facilitating agent is a cationic lipid.

82. The composition of claim 81, wherein said cationic lipid is selected from the group consisting of DMRIE, GAP-DMORIE and GAP-DLRIE.

83. The composition of claim 81, wherein said cationic lipid further comprises one or more co-lipids.

84. The composition of claim 83, wherein said co-lipids are selected from the group consisting of DOPE, DPyPE, and DMPE.

85. The composition of claim 84, comprising GAP-DLRIE and DOPE.

86. The composition of claim 83, wherein the cationic lipid:co-lipid molar ratio ranges from about 2:1 to 1:2.

87. The composition of claim 86, wherein the cationic lipid:co-lipid molar ratio is about 1:1.

88. A method for delivering a polypeptide to a vertebrate, comprising administering into a tissue or cavity of said vertebrate the composition of claim 58; wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

89. The method of claim 88; wherein said polypeptide is a therapeutic polypeptide; wherein said vertebrate is in need of the therapy provided by said polypeptide; and wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

90. The method of claim 88, wherein said polypeptide is an immunogenic or immunomodulatory polypeptide; wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

91. The method of claim 88, wherein said polypeptide is a functional self polypeptide; wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and wherein said functional self

polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

92. The method of claim 88, wherein said vertebrate is a mammal.

93. The method of claim 92, wherein said mammal is a human.

94. The method of claim 88, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue, intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

95. The method of claim 88, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

96. The method of claim 88, wherein said cavity comprises a mucosal surface.

97. The method of claim 96, wherein said mucosal surface is lung tissue.

98. The method of claim 94, wherein said tissue is muscle.

99. The method of claim 98, wherein said tissue is skeletal muscle, smooth muscle, or myocardium.

100. The method of claim 88, wherein said administration is by a route selected from the group consisting of intramuscular, intravenous, intratracheal, intranasal, transdermal, interdermal, subcutaneous, intraocular, vaginal, rectal, intraperitoneal, intraintestinal and inhalation.

101. The method of claim 88, wherein said administration route is intravenous.

102. The method of claim 88, wherein said administration route is intramuscular.

103. The method of claim 102, wherein said administration is by intramuscular injection.

104. The method of claim 88, wherein said administration is mediated by a catheter.

105. A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 58.

106. A pharmaceutical kit comprising: (a) a container holding about 1 ng to about 30 mg of a polynucleotide which operably encodes a polypeptide within vertebrate cells in vivo; and (b) an auxiliary agent selected from the group consisting of Nonidet® P40, Triton X-100.TM., Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic(® L92, Pluronic® 17R4, Pluronic® 25R4 and Pluronic® 25R2; whereby said polynucleotide is provided in a prophylactically or therapeutically effective amount to treat a vertebrate.

107. The pharmaceutical kit of claim 106, wherein (b) is in the container of (a).

108. The pharmaceutical kit of claim 106, wherein (b) is in a separate container from (a).

109. The pharmaceutical kit of claim 106, further comprising an administration means.

110. A composition comprising: (a) about 1 ng to about 30 mg of a polynucleotide in aqueous solution which operably encodes a polypeptide upon delivery to vertebrate cells in vivo, wherein said polynucleotide is complexed with a cationic lipid; (b) a salt M-X dissolved in said aqueous solution at a molar concentration ranging from about 0.1 mM to about 50 mM, and reaction, association, and dissociation products thereof, wherein M is a cation selected from the group consisting of sodium and potassium, wherein X is an anion selected from the group consisting of phosphate, acetate, bicarbonate, sulfate, and pyruvate; and wherein said aqueous solution is substantially free of chloride anion.

111. The composition of claim 110, wherein M-X is present at a molar concentration of about 1 mM to about 20 mM.

112. The composition of claim 111, wherein M-X is present at a molar concentration of about 1 mM to about 5 mM.

113. The composition of claim 112, wherein M-X is present at a molar concentration of about 2.5 mM.

114. The composition of claim 110, wherein M is sodium or potassium, and B is phosphate.

115. The composition of claim 110, wherein said cationic lipid is selected from the group consisting of DMRIE, GAP-DMORIE and GAP-DLRIE.

116. The composition of claim 110, wherein said cationic lipid further comprises one or more co-lipids.

117. The composition of claim 116, wherein said co-lipids are selected from the group consisting of DOPE, DPyPE, and DMPE.

118. The composition of claim 117, comprising GAP-DLRIE and DOPE.

119. The composition of claim 116, wherein the cationic lipid:co-lipid molar ratio ranges from about 2:1 to 1:2.

120. The composition of claim 119, wherein the cationic lipid:co-lipid molar ratio is about 1:1.

121. The composition of claim 110, wherein said polynucleotide is DNA operably associated with a promoter

122. The composition of claim 121, wherein said polynucleotide is contained on a **plasmid**.

123. The composition of claim 110, wherein said polynucleotide is RNA.

124. The composition of claim 123, wherein said polynucleotide is contained in messenger RNA.

125. The composition of claim 110, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an antigenic polypeptide, an immunogenic polypeptide, an immunomodulatory polypeptide, and a functional self polypeptide.

126. The composition of claim 125, wherein said therapeutic polypeptide is selected from the group consisting of granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10, interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, Leishmania elongation initiating factor, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, insulin, and therapeutically active fragments, derivatives, and analogs thereof.

127. The composition of claim 125, wherein said antigenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and antigenic fragments, analogs, and derivatives thereof.

128. The composition of claim 125, wherein said immunogenic polypeptide is selected from the group consisting of a bacterial polypeptide, a viral polypeptide, a fungal polypeptide, a parasite polypeptide, an allergenic polypeptide, a tumor specific polypeptide, and immunogenic fragments, analogs, and derivatives thereof.

129. The composition of claim 125, wherein said immunomodulatory polypeptide is selected from the group consisting of a cytokine, a chemokine, and immunomodulatory fragments, analogs, or derivatives thereof.

130. The composition of claim 125, wherein said functional self polypeptide is selected from the group consisting of insulin, dystrophin, cystic fibrosis transmembrane conductance regulator, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, macrophage colony stimulating factor colony stimulating factor, interleukin 2, interleukin-3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 10 interleukin 12, interleukin 15, interleukin 18, interferon alpha, interferon beta, interferon gamma, interferon omega, interferon tau, interferon gamma inducing factor I, transforming growth factor beta, RANTES, macrophage inflammatory proteins, platelet derived growth factor, tumor necrosis factor, epidermal growth factor, vascular epithelial growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, neurotrophin-2, neurotrophin-3, neurotrophin-4, neurotrophin-5, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, erythropoietin, and therapeutically active fragments, analogs, or derivatives thereof.

131. The composition of claim 111, further comprising a transfection facilitating agent selected from the group consisting of calcium phosphate, alum, gold, tungsten, or other metal particles, peptides, proteins, and polymers.

132. The composition of claim 111, further comprising an auxiliary agent selected from the group consisting of a surfactant, a detergent, a polysaccharide, a chelator, a DNase inhibitor, and a condensing agent.

133. The composition of claim 132, wherein said auxiliary agent selected from the group consisting of Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® F127, Pluronic® P65, Pluronic® P85, Pluronic® F103, Pluronic® P104, Pluronic® P105, Pluronic® P123, Pluronic® L31, Pluronic® L43, Pluronic®

Pluronic® L81, Pluronic® L92, Pluronic® L101, Pluronic® L121, Pluronic® R 17R4, Pluronic® R 25R4, Pluronic® R 25R2, IGEPAL CA 630®, NONIDET NP-40, Nonidet® P40, Tween-20®, Tween-80®, Triton X-100.TM., Triton X-114.TM., Thesit®; sodium dodecyl sulfate (SDS); stachyose; dimethylsulfoxide (DMSO); and EDTA.

134. The composition of claim 133, wherein said auxiliary agent is selected from the group consisting of Nonidet® P40, Triton X-100.TM., Pluronic® F68, Pluronic® F77, Pluronic® F108, Pluronic® P65, Pluronic® F103, Pluronic® L31, Pluronic® L44, Pluronic® L61, Pluronic® L64, Pluronic® L92, Pluronic® R 17R4, Pluronic® R 25R4 and Pluronic® R 25R2.

135. The composition of claim 134, wherein said auxiliary agent is Pluronic® R 25R2.

136. The composition of claim 134, comprising an amount of auxiliary agent selected from the group consisting of about about 0.01% (v/v) to about 0.1% (v/v) of NONIDET NP-40®; about 0.006% (v/v) to about 0.1% (v/v) of Triton X-100.TM.; about 0.1% (w/v) to about 6.0% (w/v) of Pluronic® F68; about 0.001% (w/v) to about 2.0% (w/v) of Pluronic® F77; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F108; about 0.01% (w/v) to about 1% (w/v) Pluronic® P65; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® F103; about 0.0005% (w/v) to about 1.0% (w/v) of Pluronic® L44; about 0.01% (w/v) to about 1.0% (w/v) of Pluronic® L64; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 17R4; about 0.002% (w/v) to about 1.0% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

137. The composition of claim 136, comprising about 0.001% (w/v) to about 1.0% (w/v) of Pluronic® R 25R2.

138. The composition of claim 136, comprising an amount of auxiliary agent selected from the group consisting of about 0.01% (v/v) to about 0.05% (v/v) of NONIDET N-P 40®; about 0.01% (v/v) to about 0.03% (v/v) of Triton X-100.TM.; about 0.5% to about 4.0% (w/v) of Pluronic® F68; about 0.1% (w/v) to about 1.7% (w/v) of Pluronic® F77; about 0.05% (w/v) to about 0.5% (w/v) of Pluronic® F108, about 0.1% (w/v) to about 1% (w/v) of Pluronic® P65; about 0.05% (w/v) to about 0.10% (w/v) of Pluronic® F103; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L31; about 0.001% (w/v) to about 0.10% (w/v) of Pluronic® L44; about 0.001% (w/v) to about 0.1% (w/v) Pluronic® L61; about 0.01% (w/v) to about 0.5% (w/v) of Pluronic® L64; about 0.001% (w/v) to about 1.0% (w/v) Pluronic® L92; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 17R4; about 0.01% (w/v) to about 0.10% (w/v) of Pluronic® R 25R4; and about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

139. The composition of claim 138, comprising about 0.001% (w/v) to about 0.1% (w/v) of Pluronic® R 25R2.

140. The composition of claim 138, comprising an amount of auxiliary agent selected from the group consisting of 0.01% NONIDET NP-40®; 0.01% (v/v) Triton X-100.TM.; 4% Pluronic® F68; 1.0% (w/v) Pluronic® F77; 0.1% (w/v) of Pluronic® F108; 0.5% (w/v) of Pluronic® P65; 0.05% (w/v) of Pluronic® F103; 0.05% (w/v) of Pluronic® L31; 0.001% (w/v) of Pluronic® L44; 0.01% (w/v) of Pluronic® L61; about 0.01% (w/v) to about 0.1% (w/v) of Pluronic® L64; 0.05% (w/v) of Pluronic® L92; 0.10% (w/v) of Pluronic® R 17R4; 0.01% (w/v) of Pluronic® R 25R4; and 0.01% (w/v) of Pluronic® R 25R2.

141. The composition of claim 140, comprising 0.01% (w/v) of Pluronic® R 25R2.

142. A method for delivering a polypeptide into a vertebrate, comprising administering into a tissue or cavity of said vertebrate the composition of claim 110; wherein said aqueous solution is substantially free of chloride anion, and wherein said polypeptide is expressed in the vertebrate in an amount sufficient to be detectable.

143. The method of claim 142; wherein said polypeptide is a therapeutic polypeptide; wherein said vertebrate is in need of the therapy provided by said polypeptide; and wherein said therapeutic polypeptide is expressed in the vertebrate in a therapeutically effective amount.

144. The method of claim 142, wherein said polypeptide is an immunogenic or immunomodulatory polypeptide; wherein said vertebrate is in need of such an enhanced or modulated immune response provided by said polypeptide; and wherein said immunogenic or immunomodulatory polypeptide is expressed in the vertebrate in a sufficient amount to induce a desired immune response.

145. The method of claim 142, wherein said polypeptide is a functional self polypeptide; wherein said vertebrate is incapable of making a sufficient amount of said polypeptide; and wherein said functional self polypeptide is expressed in the vertebrate in a sufficient amount to supply the vertebrate's requirements for said polypeptide.

146. The method of claim 142, wherein said vertebrate is a mammal.

147. The method of claim 142, wherein said mammal is a human.

148. The method of claim 142, wherein said tissue is selected from the group consisting of muscle, skin, brain tissue, lung tissue, liver tissue, spleen tissue, bone marrow tissue, thymus tissue, heart tissue, lymph tissue, blood tissue, bone tissue, connective tissue, mucosal tissue, pancreas tissue, kidney tissue, gall bladder tissue, intestinal tissue, testicular tissue, ovarian tissue, uterine tissue, vaginal tissue, rectal tissue, nervous system tissue, eye tissue, glandular tissue, and tongue tissue.

149. The method of claim 142, wherein said cavity is selected from the group consisting of the lungs, the mouth, the nasal cavity, the stomach, the peritoneal cavity, the intestine, a heart chamber, veins, arteries, capillaries, lymphatic cavities, the uterine cavity, the vaginal cavity, the rectal cavity, joint cavities, ventricles in brain, spinal canal in spinal cord, and the ocular cavities.

150. The method of claim 142, wherein said cavity comprises a mucosal surface.

151. The method of claim 149, wherein said mucosal surface is lung tissue.

152. The method of claim 142, wherein said administration is by a route selected from the group consisting of intravenous, intratracheal, intranasal, transdermal, intramuscular, interdermal, subcutaneous, intraocular, vaginal, rectal and inhalation.

153. The method of claim 142, wherein said administration route is intravenous.

154. The method of claim 153, wherein said administration route is intratracheal.

155. The method of claim 153, wherein said administration route is intranasal.

156. The method of claim 142, wherein said administration is mediated by

a catheter.

157. The method of claim 142, wherein said administration is by injection.

158. A method of reducing the amount of polynucleotide required to obtain a desired clinical response in a vertebrate, comprising administering to the vertebrate the composition of claim 110.

159. A pharmaceutical kit comprising: (a) a container holding about 1 ng to about 30 mg of a polynucleotide which operably encodes a polypeptide within vertebrate cells in vivo; (b) an amount of a salt M-X which, when dissolved in an prescribed volume of distilled water, results in an aqueous solution with a molar concentration of said salt from about 0.1 mM to about 150 mM, and reaction, association, or dissociation products thereof, where M is a cation selected from the group consisting of sodium and potassium, wherein X is an anion selected from the group consisting of phosphate, acetate, bicarbonate, sulfate, and pyruvate, and wherein the aqueous solution formed thereby is essentially free of chloride anion; (c) a cationic lipid; whereby said polynucleotide is provided in a prophylactically or therapeutically effective amount to treat a vertebrate.

160. The pharmaceutical kit of claim 159, wherein (b) is in the container as (a).

161. The pharmaceutical kit of claim 159, wherein (c) is in the same container as (a).

162. The pharmaceutical kit of claim 159, wherein (b) and (c) are in the same container as (a).

163. The pharmaceutical kit of claim 159, further comprising an administration means.

L36 ANSWER 37 OF 49 USPATFULL on STN
2002:12788 Method of inducing a **CTL** response.
Kundig, Thomas M., Zurich, SWITZERLAND
Simard, John J. L., Northridge, CA, UNITED STATES
US 2002007173 A1 20020117
APPLICATION: US 2001-776232 A1 20010202 (9) <--
PRIORITY: CA 1997-2209815 19970710
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein are methods for inducing an immunological **CTL** response to an antigen by sustained, regular delivery of the antigen to a mammal so that the antigen reaches the lymphatic system. Antigen is delivered at a level sufficient to induce an immunologic **CTL** response in a mammal and the level of the antigen in the mammal's lymphatic system is maintained over time sufficient to maintain the immunologic **CTL** response. Also disclosed is an article of manufacture for delivering an antigen that induces a **CTL** response in an animal.

CLM What is claimed is:

1. A method of inducing and/or sustaining an immunological **CTL** response in a mammal, which method comprises: delivering an antigen in the form of a polypeptide directly to the lymphatic system of the mammal at a level sufficient to induce an immunologic **CTL** response in the mammal; and maintaining the level of the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic **CTL** response.

2. The method of claim 1, wherein said antigen is provided as an 8-10 amino acid peptide.

3. The method of claim 1, wherein the peptide sequence is derived from a

tumor-associated antigen.

4. The method of claim 3, wherein said tumor-associated antigen is selected from the group consisting of MelanA (MART-I), gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15(58), CEA, RAGE, NY-ESO (LAGE), SCP-1, Hom/Mel-40, PRAME, p53, H-Ras, HER-2/neu, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, Epstein Barr virus antigens, EBNA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β-Catenin, CDK4, Mum-1, p16, TAGE, PSMA, PSCA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, alpha-fetoprotein , β-HCG, BCA225, BTAA, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TAG72, TLP, and TPS.

5. The method of claim 1, wherein the peptide sequence is derived from a microbial antigen.

6. The method of claim 1, wherein said antigen is provided as a component of a microorganism or mammalian cell.

7. The method of claim 6, wherein said microorganism is a protozoan.

8. The method of claim 6, wherein said microorganism is a bacterium.

9. The method of claim 6, wherein said microorganism is a virus.

10. The method of claim 6, wherein said mammalian cell is an antigen presenting cell.

11. The method of claim 10, wherein said antigen presenting cell is a dendritic cell.

12. The method of claim 6, wherein said antigen is a native component of said microorganism or mammalian cell.

13. The method of claim 6, wherein said microorganism or mammalian cell comprises an **exogenous** antigen.

14. The method of claim 6, wherein said microorganism or mammalian cell comprises a recombinant nucleic acid encoding or promoting expression of said antigen.

15. The method of claim 13, wherein said microorganism or mammalian cell expresses a tumor-associated antigen.

16. The method of claim 13, wherein said microorganism or mammalian cell expresses a microbial antigen native to a second microbial species.

17. The method of claim 13, wherein said antigen is provided as an 8-10 amino acid peptide.

18. A method of inducing and/or sustaining an immunological **CTL** response in a mammal, which method comprises: delivering an antigen, in the form of a vector comprising a nucleic acid encoding the antigen, directly to the lymphatic system of the mammal at a level sufficient to induce an immunologic **CTL** response in the mammal; and maintaining the level of the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic **CTL** response.

19. The method of claim 18, wherein the vector comprises a **plasmid**.

20. The method of claim 19, wherein the vector further comprises a bacterium.

21. The method of claim 20, wherein the bacterium is selected from the group consisting of Listeria, Shigella, Salmonella, and Escherichia.

22. The method of claim 18, wherein the vector further comprises a virus.

23. The method of claim 22, wherein the virus is selected from the group consisting of pox viruses, adenoviruses, adeno-associated viruses, retroviruses, and herpesviruses.

24. The method of claim 18, wherein said nucleic acid encodes a tumor-associated antigen.

25. The method of claim 24, wherein said tumor-associated antigen is selected from the group consisting of MelanA (MART-I), gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15(58), CEA, RAGE, NY-ESO (LAGE), SCP-1, Hom/Mel-40, PRAME, p53, H-Ras, HER-2/neu, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, Epstein Barr virus antigens, EBNA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β-Catenin, CDK4, Mum-1, p16, TAGE, PSMA, PSCA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, alpha-fetoprotein , β-HCG, BCA225, BTAA, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TAG72, TLP, and TPS.

26. The method of claim 18, wherein said nucleic acid encodes a microbial antigen.

27. The method of claim 26, wherein said antigen is a viral antigen.

28. The method of claim 26, wherein said antigen is a bacterial antigen.

29. The method of claim 26, wherein said antigen is a protozoal antigen.

30. The method of claim 18, wherein said nucleic acid encodes a protein or other polypeptide.

31. The method of claim 30, wherein said nucleic acid encodes an 8-10 amino acid peptide.

32. The method of claim 18, wherein said nucleic acid is **plasmid** DNA in a formulation comprising about 1-10% ethyl alcohol, 0-1% benzyl alcohol, 0.25-0.5 mM EDTA and a citrate-phosphate buffer of pH 7.4-7.8, comprising about 3-50 mM citrate and about 90 -200 mM phosphate.

33. The method of claim 32, wherein said formulation comprises 1% ethyl alcohol, 1% benzyl alcohol, 0.5 mM EDTA and a citrate-phosphate buffer of pH 7.4 to 7.8 comprising 50 mM citrate and 100 mM phosphate.

34. A method of inducing and/or sustaining an immunological **CTL** response in a mammal, which method comprises: delivering a microorganism or mammalian cell directly to the lymphatic system of the mammal at a level sufficient to induce an immunologic **CTL** response in the mammal; and maintaining the level of the microorganism or mammalian cell in the mammal's lymphatic system over time sufficient to maintain the immunologic **CTL** response.

35. A method of inducing and/or sustaining an immunological **CTL** response in a mammal, which method comprises: delivering a nucleic acid capable of conferring antigen expression, directly to the lymphatic system of the mammal at a level sufficient to induce an immunologic **CTL** response in the mammal; and maintaining the level of the nucleic

held in the mammal's lymphatic system over time sufficient to maintain the immunologic **CTL** response.

36. A method of inducing and/or sustaining an immunological **CTL** response in a mammal, which method comprises: delivering a non-peptide antigen directly to the lymphatic system of the mammal at a level sufficient to induce an immunologic **CTL** response in the mammal; and maintaining the level of the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic **CTL** response.

37. An article of manufacture for delivering an antigen that induces a **CTL** response in an animal, wherein the article is an external device, and which article comprises: a reservoir of a physiologically-acceptable, antigen-containing composition that is capable of inducing a **CTL** response in an animal; a pump connected to the reservoir to deliver the composition at a defined rate; a transmission line to discharge the composition from the reservoir; and, a delivery line connected to the transmission line, which delivery line comprises a catheter of at least 20 mm for positioning in the animal and for delivery of the composition to the lymphatic system of the animal.

L36 ANSWER 47 OF 49 USPATFULL on STN
1999:96351 DNA vaccination for induction of suppressive T cell response.
Steinman, Lawrence, Palo Alto, CA, United States
Waisman, Ari, Tel-Aviv, Israel
The Board of Trustees of The Leland Stanford Junior University, Palo Alto, CA, United States (U.S. corporation)
US 5939400 19990817
APPLICATION: US 1996-606639 19960226 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pro-inflammatory T response is specifically prevented by the injection into a recipient of DNA encoding the variable region of a T cell receptor. In response to the vaccination, T cells expressing the variable region produce Th2 cytokines, including IL-4. A pro-inflammatory T cell response directed to an autoantigen is shown to be suppressed by DNA vaccination. The suppressive vaccination further reduced the inflammatory effect of T cells reactive against epitopes of the autoantigen not recognized by the variable region used for vaccination.
CLM What is claimed is:
1. A method of suppressing Th1 type T cell response in a myelin basic protein associated autoimmune disease, the method comprising: injecting into muscle tissue of a mammalian host a DNA expression vector comprising: a sequence encoding the variable region of a T cell receptor that (a) is selected from the group consisting of mouse Vβ8.2, mouse Vβ17a, human Vβ5, human Vβ6, human Vβ4 subfamily and human Vβ12 subfamily, (b) recognizes an epitope of myelin basic protein, and (c) is under the regulatory control of a promoter that is active in said muscle tissue, wherein said expression cassette is incorporated into muscle cells of said host and said sequence is expressed at levels sufficient to suppress said Th1 type T cell response, and wherein said suppression of the TH1 type T cell response prevents onset of said myelin basic protein associated autoimmune disease.

2. A method according to claim 1, further comprising the step of injecting cardiotoxin into said muscle tissue, prior to said introducing step.

3. A method according to claim 1, wherein said DNA expression vector is a **plasmid**.

4. A method according to claim 3, wherein said **plasmid** is transiently expressed in said muscle cells.

5. A method according to claim 1, wherein said mammalian host is a mouse and wherein said sequence encoding the variable region of a T cell receptor is mouse Vβ8.2.

6. A method according to claim 1, wherein said autoimmune disease is multiple sclerosis.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
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L29            7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30         2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31         1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32          795 S L31 AND EXOGENOUS
L33          790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34           77 S L33 AND PLASMID/CLM
L35           11 S L34 AND PY<2002
L36           49 S L34 AND AY<2002

=> file medline
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        51.72     146.86

FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004

 FILE LAST UPDATED: 28 APR 2004 (20040428/UP).  FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (DNA-based immunization or gene vaccination)
        740828 DNA
        618515 BASED
         85697 IMMUNIZATION
           111 DNA-BASED IMMUNIZATION
                 (DNA(W)BASED(W)IMMUNIZATION)
        679604 GENE
         62314 VACCINATION
            27 GENE VACCINATION
                 (GENE(W)VACCINATION)
L37          138 (DNA-BASED IMMUNIZATION OR GENE VACCINATION)

=> s l37 and dendritic
         30527 DENDRITIC
L38           10 L37 AND DENDRITIC

=> d l38,ti,1-10

L38  ANSWER 1 OF 10     MEDLINE on STN
TI   What's new in the treatment of advanced prostate cancer?.

L38  ANSWER 2 OF 10     MEDLINE on STN
TI   DNA-encoded fetal liver tyrosine kinase 3 ligand and granulocyte
     macrophage-colony-stimulating factor increase dendritic cell recruitment
     to the inoculation site and enhance antigen-specific CD4+ T cell responses
     induced by DNA vaccination of outbred animals.

L38  ANSWER 3 OF 10     MEDLINE on STN
TI   Generation of potent and specific cellular immune responses via in vivo
     stimulation of dendritic cells by pNGVL3-hFLex plasmid DNA and
     immunogenic peptides.

L38  ANSWER 4 OF 10     MEDLINE on STN
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prime-adenovirus boost genetic vaccination.

L38 ANSWER 5 OF 10 MEDLINE on STN
TI Mechanism and therapeutic potential of **DNA-based immunization** against the envelope proteins of hepatitis B virus in normal and transgenic mice.

L38 ANSWER 6 OF 10 MEDLINE on STN
TI Direct transfection and activation of human cutaneous **dendritic** cells.

L38 ANSWER 7 OF 10 MEDLINE on STN
TI DNA immunization targeting the skin: molecular control of adaptive immunity.

L38 ANSWER 8 OF 10 MEDLINE on STN
TI Specific immune induction following **DNA-based immunization** through in vivo transfection and activation of macrophages/antigen-presenting cells.

L38 ANSWER 9 OF 10 MEDLINE on STN
TI Autologous human monocyte-derived **dendritic** cells genetically modified to express melanoma antigens elicit primary cytotoxic T cell responses in vitro: enhancement by cotransfection of genes encoding the Th1-biasing cytokines IL-12 and IFN-alpha.

L38 ANSWER 10 OF 10 MEDLINE on STN
TI **DNA-based immunization** by in vivo transfection of **dendritic** cells.

=> d l38,cbib,ab,5,8,10

L38 ANSWER 5 OF 10 MEDLINE on STN
2001296029. PubMed ID: 11380696. Mechanism and therapeutic potential of **DNA-based immunization** against the envelope proteins of hepatitis B virus in normal and transgenic mice. Oka Y; Akbar S M; Horiike N; Joko K; Onji M. (Third Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan.) Immunology, (2001 May) 103 (1) 90-7. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB Two plasmid DNA vectors, pCAGGS(S) encoding the genes of the major envelope protein of hepatitis B virus (HBV), and pCAGGS(S + preS2) encoding the genes of the middle envelope protein were used to study the mechanism and therapeutic potential of **DNA-based immunization**. Injection of these plasmids into the regenerating bilateral tibialis anterior muscle (TA) of normal C57BL/6 mice induced hepatitis B surface antigen (HBsAg)-specific humoral and cellular immune responses. Seventy-two hours after injection of pCAGGS(S), infiltrating cells including antigen-presenting **dendritic** cells (DC) were localized around the injection site and HBsAg was expressed by both muscle cells and infiltrating cells. Spleen DC from the mice were exposed to HBsAg for up to 32 weeks after a single injection of pCAGGS(S), because these DC induced the proliferation of HBsAg-specific memory lymphocytes in culture without exogenous HBsAg. A single injection of pCAGGS(S) or pCAGGS(S + preS2) resulted in the clearance of HBsAg in 28 out of 30 HBV-transgenic (Tg) mice. In contrast, more than 7 monthly injections of an HBsAg-based vaccine were required for the clearance of HBsAg in 6 out of 29 HBV-Tg mice. Infiltrating DC at the DNA vaccine injection site may have a role in initiating HBsAg-specific immune response, whereas the persistence of HBsAg exposed spleen DC may contribute to long-lasting immunity. This study also suggested that DNA-based vaccines may be a potent tool for treating chronic HBV carriers.

L38 ANSWER 8 OF 10 MEDLINE on STN
1998299592. PubMed ID: 9637479. Specific immune induction following **DNA-based immunization** through in vivo transfection and activation

Boyer J D; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Journal of immunology (Baltimore, Md. : 1950), (1998 Jun 15) 160 (12) 5707-18. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The initiation of an adaptive immune response requires Ag presentation in combination with the appropriate activation signals. Classically, Ag presentation and immune activation occur in the lymph node and spleen, where a favorable organ architecture and rich cellular help can enhance the process. Recently, several investigators have reported the use of DNA expression cassettes to elicit cellular and humoral immunity against diverse pathogens. Although the immune mechanisms involved are still poorly understood, plasmid inoculation represents a model system for studying immune function in response to invading pathogens. In this report, we demonstrate the presence of activated macrophages or **dendritic** cells in the blood lymphocyte pool and peripheral tissues of animals inoculated with DNA expression cassettes. These cells are directly transfected in vivo, present Ag, and display the surface proteins CD80 and CD86. Our studies indicate that these cells function as APC and can activate naive T lymphocytes. They may represent an important first step APC in genetic immunization and natural infection.

L38 ANSWER 10 OF 10 MEDLINE on STN

96434687. PubMed ID: 8837611. **DNA-based immunization** by in vivo transfection of **dendritic** cells. Condon C; Watkins S C; Celluzzi C M; Thompson K; Falo L D Jr. (Department of Dermatology, University of Pittsburgh School of Medicine, Pennsylvania 15213, USA.) Nature medicine, (1996 Oct) 2 (10) 1122-8. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Delivery of antigen in a manner that induces effective, antigen-specific immunity is a critical challenge in vaccine design. Optimal antigen presentation is mediated by professional antigen-presenting cells (APCs) capable of taking up, processing and presenting antigen to T cells in the context of costimulatory signals required for T-cell activation. Developing immunization strategies to optimize antigen presentation by **dendritic** cells, the most potent APCs, is a rational approach to vaccine design. Here we show that cutaneous genetic immunization with naked DNA results in potent, antigen-specific, cytotoxic T lymphocyte-mediated protective tumor immunity. This method of immunization results in the transfection of skin-derived **dendritic** cells, which localize in the draining lymph nodes. These observations provide a basis for further development of DNA-based vaccines and demonstrate the feasibility of genetically engineering **dendritic** cells in vivo.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
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L8             6 S E3
L9             5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                   E SCHWARTZ OLIVIER/IN
                   E SCHWARTZ O/IN
L10           16 S E3-E5
                   E BUSEYNE F/IN
L11            1 S E3
L12            0 S L11 NOT L10
                   E MARSAC D/IN
L13            2 S E3
L14            1 S L13 NOT L10
                   E RIVIERE Y/IN
L15            7 S E3 OR E4
L16            6 S L15 NOT L10
                   E HEARD J/IN
L17            2 S E8
L18            2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                   E SCHWARTZ O/AU
L19           10 S E7
L20           90 S E3
L21            2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                   E BUSEYNE F/AU
L22           25 S E3 OR E4
L23           21 S L22 NOT L20
                   E MARSAC E/AU
L24            1 S E2
L25            0 S L24 NOT L20
                   E RIVIERE Y/AU
L26          104 S E3 OR E4
L27          101 S L26 NOT L20
                   E HEARD J M/AU
L28            7 S E8
L29            7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                   E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30         2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31         1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32          795 S L31 AND EXOGENOUS
L33          790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34           77 S L33 AND PLASMID/CLM
L35           11 S L34 AND PY<2002
L36           49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37          138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38           10 S L37 AND DENDRITIC

=> s l38 and (gene vaccination)
        679819 GENE
         62327 VACCINATION
            27 GENE VACCINATION
                 (GENE(W)VACCINATION)
L39            1 L38 AND (GENE VACCINATION)

=> d l39,cbib,ab

L39  ANSWER 1 OF 1     MEDLINE on STN
2003003933.    PubMed ID: 12509944.   What's new in the treatment of advanced
     prostate cancer?. Sternberg C N. (Chief, Department of Medical Oncology,
     San Camillo-Forlanini Hospital, Vincenzo Pansadoro Foundation, Via Aurelia
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(Oxford, England : 1990), (2003 Jan) 39 (2) 136-46. Ref: 107. Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.

AB Increased insight into the biology of prostate cancer and the emergence of new therapeutic strategies and chemotherapeutic agents has changed approaches in treating patients with advanced prostate cancer. After secondary hormonal manipulations, new approaches include: second-line hormonal therapy, chemotherapy, immunotherapy with granulocyte macrophage-colony stimulating factor (GM-CSF) therapy, **dendritic** cell therapy, **gene vaccination** therapy, inhibition and/or blockade of growth factor receptors or growth factor receptor pathways, inhibition of neo-angiogenesis and inhibition of invasion and metastases.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

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     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
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L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
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L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
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L19          10 S E7
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L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
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                  E RIVIERE Y/AU
L26           104 S E3 OR E4
L27           101 S L26 NOT L20
                  E HEARD J M/AU
L28             7 S E8
L29             7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
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L30          2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31          1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32           795 S L31 AND EXOGENOUS
L33           790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34            77 S L33 AND PLASMID/CLM
L35            11 S L34 AND PY<2002
L36            49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37           138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38            10 S L37 AND DENDRITIC
L39             1 S L38 AND (GENE VACCINATION)

=> s (naked plasmid DNA)
          3530 NAKED
         54046 PLASMID
        741015 DNA
L40          181 (NAKED PLASMID DNA)
                   (NAKED(W)PLASMID(W)DNA)

=> s l40 and py=1996
        422579 PY=1996
L41           11 L40 AND PY=1996

=> d l41,ti,1-11
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L41 ANSWER 1 OF 11 MEDLINE on STN
TI Naked cDNA encoding secreted proteins for intra-arterial and intramuscular gene transfer.

L41 ANSWER 2 OF 11 MEDLINE on STN
TI Direct intramuscular gene transfer of naked DNA encoding vascular endothelial growth factor augments collateral development and tissue perfusion.

L41 ANSWER 3 OF 11 MEDLINE on STN
TI A little VEGF goes a long way. Therapeutic angiogenesis by direct injection of vascular endothelial growth factor-encoding plasmid DNA.

L41 ANSWER 4 OF 11 MEDLINE on STN
TI Gene vaccination with **naked plasmid DNA**: mechanism of CTL priming.

L41 ANSWER 5 OF 11 MEDLINE on STN
TI Naked DNA delivered intraportally expresses efficiently in hepatocytes.

L41 ANSWER 6 OF 11 MEDLINE on STN
TI Direct gene transfer to mouse melanoma by intratumor injection of free DNA.

L41 ANSWER 7 OF 11 MEDLINE on STN
TI HHR23B, a human Rad23 homolog, stimulates XPC protein in nucleotide excision repair in vitro.

L41 ANSWER 8 OF 11 MEDLINE on STN
TI Long-term expression of a fluorescent reporter gene via direct injection of plasmid vector into mouse skeletal muscle: comparison of human creatine

L41 ANSWER 9 OF 11 MEDLINE on STN
TI Characterization of plasmid DNA transfer into mouse skeletal muscle: evaluation of uptake mechanism, expression and secretion of gene products into blood.

L41 ANSWER 10 OF 11 MEDLINE on STN
TI In vivo gene transfer and expression in rat stomach by submucosal injection of plasmid DNA.

L41 ANSWER 11 OF 11 MEDLINE on STN
TI Direct gene delivery to synovium. An evaluation of potential vectors in vitro and in vivo.

=> d l41,cbib,ab,4

L41 ANSWER 4 OF 11 MEDLINE on STN
97033532. PubMed ID: 8879229. Gene vaccination with **naked plasmid DNA**: mechanism of CTL priming. Corr M; Lee D J; Carson D A; Tighe H. (Department of Medicine, University of California, San Diego, La Jolla 92093-0663, USA.) Journal of experimental medicine, **(1996 Oct 1)** 184 (4) 1555-60. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The injection of **naked plasmid DNA** directly into the muscle cells of mice has been shown to induce potent humoral and cellular immune responses. The generation of a cytotoxic T lymphocyte (CTL) response after plasmid DNA injection may involve the presentation of the expressed antigen in the context of the injected myocytes' endogenous major histocompatibility (MHC)-encoded class I molecules or may use the MHC molecules of bone marrow-derived antigen presenting cells (APC) which are capable of providing co-stimulation as well. To resolve which cell type provides the specific restricting element for this method of vaccination we generated parent-->F1 bone marrow chimeras in which H-2bxd recipient mice received bone marrow that expressed only H-2b or H-2d MHC molecules. These mice were injected intramuscularly with **naked plasmid DNA** that encoded the nucleoprotein from the A/PR/8/34 influenza strain, which as a single antigen has epitopes for both H-2Db and H-2Kd. The resulting CTL responses were restricted to the MHC haplotype of the bone marrow alone and not to the second haplotype expressed by the recipient's myocytes. The role of somatic tissues that express protein from injected plasmids may be to serve as a reservoir for that antigen which is then transferred to the APC. Consequently, our data show that the mechanism of priming in this novel method for vaccination uses the MHC from bone marrow-derived APC, which are efficient at providing all of the necessary signals for priming the T cell.

=> d his

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     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
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L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
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                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
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L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
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L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37         138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38          10 S L37 AND DENDRITIC
L39           1 S L38 AND (GENE VACCINATION)
L40         181 S (NAKED PLASMID DNA)
L41          11 S L40 AND PY=1996

=> s l40 and dendritic
        30544 DENDRITIC
L42           5 L40 AND DENDRITIC

=> d l42,ti,1-5

L42  ANSWER 1 OF 5     MEDLINE on STN
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precursors.

L42 ANSWER 2 OF 5 MEDLINE on STN
TI Gene therapy of autoimmune diseases with vectors encoding regulatory cytokines or inflammatory cytokine inhibitors.

L42 ANSWER 3 OF 5 MEDLINE on STN
TI **Dendritic** cells in genetic immunization.

L42 ANSWER 4 OF 5 MEDLINE on STN
TI Enhancement of immune response to naked DNA vaccine by immunization with transfected **dendritic** cells.

L42 ANSWER 5 OF 5 MEDLINE on STN
TI Intradermal gene immunization: the possible role of DNA uptake in the induction of cellular immunity to viruses.

=> d l42,cbib,ab,1-4

L42 ANSWER 1 OF 5 MEDLINE on STN
2002423685. PubMed ID: 12180545. Genetic immunization using nanoparticles engineered from microemulsion precursors. Cui Zhengrong; Mumper Russell J. (Division of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington 40536-0082, USA.) Pharmaceutical research, (2002 Jul) 19 (7) 939-46. Journal code: 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.
AB PURPOSE: Genetic immunization using **"naked" plasmid DNA** (pDNA) has been shown to elicit broad humoral and cellular immune responses. However, more versatile and perhaps cell-targeted delivery systems are needed. To this end, a novel process to engineer cationic nanoparticles coated with pDNA for genetic immunization was explored. METHODS; Cationic nanoparticles were engineered from warm oil-in-water microemulsion precursors composed of emulsifying wax as the oil phase and cetyltrimethylammonium bromide (CTAB) as the cationic surfactant. Plasmid DNA was coated on the surface of the cationic nanoparticles to produce pDNA-coated nanoparticles. An endosomolytic lipid and/or a **dendritic** cell-targeting ligand (mannan) were incorporated in or deposited on the nanoparticles to enhance the in vitro cell transfection efficiency and the in vivo immune responses after subcutaneous injection to Balb/C mice. The IgG titer to expressed beta-galactosidase and the cytokine release from isolated splenocytes after stimulation were determined on 28 days. RESULTS: Cationic nanoparticles (around 100 nm) were engineered within minutes. The pDNA-coated nanoparticles were stable at 37 degrees C over 30 min in selected biologic fluids. Transmission electron microscopy showed the nanoparticles were spherical. Plasmid DNA-coated nanoparticles. especially those with both an endosomolytic lipid and **dendritic** cell-targeting ligand. resulted in significant enhancement in both IgG titer (over 16-fold) and T-helper type-1 (Th1-type) cytokine release (up to 300% increase) over "naked" pDNA. CONCLUSION: A novel method to engineer pDNA-coated nanoparticles for enhanced in vitro cell transfection and enhanced in vivo immune responses was reported.

L42 ANSWER 2 OF 5 MEDLINE on STN
2001121552. PubMed ID: 10953913. Gene therapy of autoimmune diseases with vectors encoding regulatory cytokines or inflammatory cytokine inhibitors. Prud'homme G J. (Department of Pathology, McGill University, Montreal, Quebec, Canada.. gprudh@po-box.mcgill.ca) . journal of gene medicine, (2000 Jul-Aug) 2 (4) 222-32. Ref: 98. Journal code: 9815764. ISSN: 1099-498X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Gene therapy offers advantages for the immunotherapeutic delivery of cytokines or their inhibitors. After gene transfer, these mediators are produced at relatively constant, non-toxic levels and sometimes in a tissue-specific manner, obviating limitations of protein administration. Therapy with viral or nonviral vectors is effective in several animal

models of autoimmunity including type 1 diabetes mellitus (DM), experimental allergic encephalomyelitis (EAE), systemic lupus erythematosus (SLE), colitis, thyroiditis and various forms of arthritis. Genes encoding transforming growth factor beta, interleukin-4 (IL-4) and IL-10 are most frequently protective. Autoimmune/ inflammatory diseases are associated with excessive production of inflammatory cytokines such as IL-1, IL-12, tumor necrosis factor alpha (TNFalpha) and interferon gamma (IFNgamma). Vectors encoding inhibitors of these cytokines, such as IL-1 receptor antagonist, soluble IL-1 receptors, IL-12p40, soluble TNFalpha receptors or IFNgamma-receptor/IgG-Fc fusion proteins are protective in models of either arthritis, Type 1 DM, SLE or EAE. We use intramuscular injection of **naked plasmid DNA** for cytokine or anticytokine therapy. Muscle tissue is accessible, expression is usually more persistent than elsewhere, transfection efficiency can be increased by low-voltage in vivo electroporation, vector administration is simple and the method is inexpensive. Plasmids do not induce neutralizing immunity allowing repeated administration, and are suitable for the treatment of chronic immunological diseases.

L42 ANSWER 3 OF 5 MEDLINE on STN

1999376420. PubMed ID: 10449180. **Dendritic** cells in genetic immunization. Takashima A; Morita A. (Department of Dermatology, University of Texas Southwestern Medical Center, Dallas 75235-9069, USA.) Journal of leukocyte biology, (1999 Aug) 66 (2) 350-6. Ref: 78. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Both humoral and cellular immune responses are inducible by inoculation of **naked plasmid DNA** encoding a polypeptide antigen. This new vaccination protocol, known as genetic immunization, has been used to initiate protective immunity against a variety of infectious pathogens and tumors in experimental animals. **Dendritic** cells (DC) are thought to play at least three distinct roles in genetic immunization: (1) MHC class II-restricted presentation of antigens secreted by neighboring, transfected cells, (2) MHC class I-restricted "cross" presentation of antigens released by neighboring, transfected cells, and (3) direct presentation of antigens by transfected DC themselves. Several new technologies have been developed recently in an attempt to improve the overall efficacy of genetic vaccination, as well as to regulate the type and class of resulting immune responses. These technologies include modification of plasmid DNA, co-delivery of genes encoding immunoregulatory molecules, and DC targeting. We will overview some of these new technologies in genetic immunization.

L42 ANSWER 4 OF 5 MEDLINE on STN

97174182. PubMed ID: 9021916. Enhancement of immune response to naked DNA vaccine by immunization with transfected **dendritic** cells. Manickan E; Kanangat S; Rouse R J; Yu Z; Rouse B T. (Department of Microbiology, College of Veterinary Medicine, University of Tennessee, Knoxville 37996-0845, USA.) Journal of leukocyte biology, (1997 Feb) 61 (2) 125-32. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Immunization with plasmid DNA encoding various proteins promises to be a valuable vaccine approach especially if its immunogenicity could be optimized. In this study we show that the intramuscular delivery in **dendritic** cells (DC) of **naked plasmid DNA** encoding two proteins of herpes simplex virus (HSV) leads to the induction of significantly enhanced levels of resistance to viral challenge. Whereas DC transfected in vitro with DNA induced enhanced immunity, similarly transfected macrophage (M phi) populations lacked immunogenicity even though plasmid expression occurred in vitro. The enhanced immunity induced by DC-delivered DNA appeared to be associated mainly with an increased Th1 CD4+ T cell response. Our results add evidence that DC are the essential antigen-presenting cell types involved in immune responses to intramuscularly administered DNA vaccines.

L42 ANSWER 2 OF 5 MEDLINE on STN
2001121552. PubMed ID: 10953913. Gene therapy of autoimmune diseases with vectors encoding regulatory cytokines or inflammatory cytokine inhibitors. Prud'homme G J. (Department of Pathology, McGill University, Montreal, Quebec, Canada.. gprudh@po-box.mcgill.ca) . journal of gene medicine, (2000 Jul-Aug) 2 (4) 222-32. Ref: 98. Journal code: 9815764. ISSN: 1099-498X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Gene therapy offers advantages for the immunotherapeutic delivery of cytokines or their inhibitors. After gene transfer, these mediators are produced at relatively constant, non-toxic levels and sometimes in a tissue-specific manner, obviating limitations of protein administration. Therapy with viral or nonviral vectors is effective in several animal models of autoimmunity including Type 1 diabetes mellitus (DM), experimental allergic encephalomyelitis (EAE), systemic lupus erythematosus (SLE), colitis, thyroiditis and various forms of arthritis. Genes encoding transforming growth factor beta, interleukin-4 (IL-4) and IL-10 are most frequently protective. Autoimmune/ inflammatory diseases are associated with excessive production of inflammatory cytokines such as IL-1, IL-12, tumor necrosis factor alpha (TNFalpha) and interferon gamma (IFNgamma). Vectors encoding inhibitors of these cytokines, such as IL-1 receptor antagonist, soluble IL-1 receptors, IL-12p40, soluble TNFalpha receptors or IFNgamma-receptor/IgG-Fc fusion proteins are protective in models of either arthritis, Type 1 DM, SLE or EAE. We use intramuscular injection of **naked plasmid DNA** for cytokine or anticytokine therapy. Muscle tissue is accessible, expression is usually more persistent than elsewhere, transfection efficiency can be increased by low-voltage in vivo electroporation, vector administration is simple and the method is inexpensive. Plasmids do not induce neutralizing immunity allowing repeated administration, and are suitable for the treatment of chronic immunological diseases.

L42 ANSWER 3 OF 5 MEDLINE on STN
1999376420. PubMed ID: 10449180. **Dendritic** cells in genetic immunization. Takashima A; Morita A. (Department of Dermatology, University of Texas Southwestern Medical Center, Dallas 75235-9069, USA.) Journal of leukocyte biology, (1999 Aug) 66 (2) 350-6. Ref: 78. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Both humoral and cellular immune responses are inducible by inoculation of **naked plasmid DNA** encoding a polypeptide antigen. This new vaccination protocol, known as genetic immunization, has been used to initiate protective immunity against a variety of infectious pathogens and tumors in experimental animals. **Dendritic** cells (DC) are thought to play at least three distinct roles in genetic immunization: (1) MHC class II-restricted presentation of antigens secreted by neighboring, transfected cells, (2) MHC class I-restricted "cross" presentation of antigens released by neighboring, transfected cells, and (3) direct presentation of antigens by transfected DC themselves. Several new technologies have been developed recently in an attempt to improve the overall efficacy of genetic vaccination, as well as to regulate the type and class of resulting immune responses. These technologies include modification of plasmid DNA, co-delivery of genes encoding immunoregulatory molecules, and DC targeting. We will overview some of these new technologies in genetic immunization.

L42 ANSWER 4 OF 5 MEDLINE on STN
97174182. PubMed ID: 9021916. Enhancement of immune response to naked DNA vaccine by immunization with transfected **dendritic** cells. Manickan E; Kanangat S; Rouse R J; Yu Z; Rouse B T. (Department of Microbiology, College of Veterinary Medicine, University of Tennessee, Knoxville 37996-0845, USA.) Journal of leukocyte biology, (1997 Feb) 61 (2) 125-32. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB Immunization with plasmid DNA encoding various proteins promises to be a

optimized. In this study we show that the intramuscular delivery in **dendritic** cells (DC) of **naked plasmid DNA** encoding two proteins of herpes simplex virus (HSV) leads to the induction of significantly enhanced levels of resistance to viral challenge. Whereas DC transfected in vitro with DNA induced enhanced immunity, similarly transfected macrophage (M phi) populations lacked immunogenicity even though plasmid expression occurred in vitro. The enhanced immunity induced by DC-delivered DNA appeared to be associated mainly with an increased Th1 CD4+ T cell response. Our results add evidence that DC are the essential antigen-presenting cell types involved in immune responses to intramuscularly administered DNA vaccines.

L42 ANSWER 5 OF 5 MEDLINE on STN
95023943. PubMed ID: 7937799. Intradermal gene immunization: the possible role of DNA uptake in the induction of cellular immunity to viruses. Raz E; Carson D A; Parker S E; Parr T B; Abai A M; Aichinger G; Gromkowski S H; Singh M; Lew D; Yankauckas M A; +. (Department of Medicine, University of California, San Diego, La Jolla 92093-0663.) Proceedings of the National Academy of Sciences of the United States of America, (1994 Sep 27) 91 (20) 9519-23. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The skin and mucous membranes are the anatomical sites were most viruses are first encountered by the immune system. Previous experiments have suggested that striated muscle cells are unique among mammalian cell types in their capacity to take up and express free DNA in the absence of a viral vector or physical carrier. However, we have found that mice injected into the superficial skin with free (**naked**) **plasmid DNA** encoding the influenza nucleoprotein gene had discrete foci of epidermal and dermal cells, including cells with **dendritic** morphology, that contained immunoreactive nucleoprotein antigen. A single intradermal administration of 0.3-15 micrograms of free plasmid DNA induced anti-nucleoprotein-specific antibody and cytotoxic T lymphocytes that persisted for at least 68-70 weeks after vaccination. Intradermal gene administration induced higher antibody titers than did direct gene injection into skeletal muscle and did not cause local inflammation or necrosis. Compared with control animals, the gene-injected mice were resistant to challenge with a heterologous strain of influenza virus. These results indicate that the cells of the skin can take up and express free foreign DNA and induce cellular and humoral immune responses against the encoded protein. We suggest that DNA uptake by the skin-associated lymphoid tissues may play a role in the induction of cytotoxic T cells against viruses and other intracellular pathogens.

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YOU HAVE RECEIVED 8 CONSECUTIVE ARROW PROMPTS (=>)
The arrow (=>) is the system prompt, where you enter a command. For an explanation of system commands, files, formats, etc., enter "HELP" and the name of the item you want explained at an arrow prompt (=>). Enter "HELP COMMANDS" for a list of commands that can be used in this file. Enter "HELP MESSAGES" for a list of online explanations that are available. The "?" can be used as a synonym for "HELP".

Help is also available at any prompt, and after any error message. Enter "HELP" or "?" at a prompt to see an explanation of the options. After an error message, enter "HELP" or "?" at the next prompt and you will receive a more detailed explanation of the error and how to correct it.

Automatic help is also available. When AUHELP is 'ON', you will automatically receive help following an error message. For more information on AUHELP, enter "HELP SET AUHELP" at an arrow prompt (=>).

Users who need additional assistance can contact the Help Desk at their nearest STN Service Center. Enter "HELP STN" for information on STN Service Centers. You may also choose to contact the database representative for the file you are searching, for more detailed help on database content and search strategy. For information on how to contact database representatives for the current file, enter "HELP DESK" at an arrow prompt (=>).
IF YOU REQUIRE FURTHER HELP, PLEASE CONTACT YOUR LOCAL HELP DESK

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
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                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
L28           7 S E8
L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37         138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38          10 S L37 AND DENDRITIC
L39           1 S L38 AND (GENE VACCINATION)
L40         181 S (NAKED PLASMID DNA)
L41          11 S L40 AND PY=1996
L42           5 S L40 AND DENDRITIC

=> s l40 and (multivalent)
        2204 MULTIVALENT
L43        0 L40 AND (MULTIVALENT)

=> s multivalent vaccine
        2204 MULTIVALENT
       81829 VACCINE
L44       80 MULTIVALENT VACCINE
              (MULTIVALENT(W)VACCINE)

=> s l44 and (genetic immunization or DNA immunization or DNA-based or gen? vaccination or plas
      485047 GENETIC
       85706 IMMUNIZATION
         247 GENETIC IMMUNIZATION
              (GENETIC(W)IMMUNIZATION)
      741015 DNA
       85706 IMMUNIZATION
         537 DNA IMMUNIZATION
              (DNA(W)IMMUNIZATION)
      741015 DNA
      618735 BASED
        1817 DNA-BASED
              (DNA(W)BASED)
     2418412 GEN?
       62327 VACCINATION
         190 GEN? VACCINATION
              (GEN?(W)VACCINATION)
       54046 PLASMID
      741015 DNA
        8103 PLASMID DNA
              (PLASMID(W)DNA)
L45        1 L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASED
             OR GEN? VACCINATION OR PLASMID DNA)

=> d l45

L45  ANSWER 1 OF 1     MEDLINE on STN
Full Text
AN   1999429594     MEDLINE
DN   PubMed ID: 10501486
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TI Lyssavirus glycoproteins expressing immunologically potent foreign B cell and cytotoxic T lymphocyte epitopes as prototypes for multivalent vaccines.
AU Desmezieres E; Jacob Y; Saron M F; Delpeyroux F; Tordo N; Perrin P
CS Laboratoire des Lyssavirus, Institut Pasteur 25, Paris, France.
SO Journal of general virology, (1999 Sep) 80 (Pt 9) 2343-51.
Journal code: 0077340. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007

=> d l45,cbib,ab

L45 ANSWER 1 OF 1 MEDLINE on STN
1999429594. PubMed ID: 10501486. Lyssavirus glycoproteins expressing immunologically potent foreign B cell and cytotoxic T lymphocyte epitopes as prototypes for multivalent vaccines. Desmezieres E; Jacob Y; Saron M F; Delpeyroux F; Tordo N; Perrin P. (Laboratoire des Lyssavirus, Institut Pasteur 25, Paris, France.) Journal of general virology, (1999 Sep) 80 (Pt 9) 2343-51. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Truncated and chimeric lyssavirus glycoprotein (G) genes were used to carry and express non-lyssavirus B and T cell epitopes for **DNA-based** immunization of mice, with the aim of developing a **multivalent vaccine** prototype. Truncated G (GPVIII) was composed of the C-terminal half (aa 253-503) of the Pasteur rabies virus (PV: genotype 1) G containing antigenic site III and the transmembrane and cytoplasmic domains. The chimeric G (GEBL1-PV) was composed of the N-terminal half (aa 1-250) of the European bat lyssavirus 1 (genotype 5) G containing antigenic site II linked to GPVIII. Antigenic sites II and III are involved in the induction of virus-neutralizing antibodies. The B cell epitope was the C3 neutralization epitope of the poliovirus type 1 capsid VP1 protein. The T cell epitope was the H2d MHC I-restricted epitope of the nucleoprotein of lymphocytic choriomeningitis virus (LCMV) involved in the induction of both cytotoxic T cell (CTL) production and protection against LCMV. Truncated G carrying foreign epitopes induced weak antibody production against rabies and polio viruses and provided weak protection against LCMV. In contrast, the chimeric plasmid containing various combinations of B and CTL epitopes elicited simultaneous immunological responses against both parental lyssaviruses and poliovirus and provided good protection against LCMV. The level of humoral and cellular immune responses depended on the order of the foreign epitopes inserted. Our results demonstrate that chimeric lyssavirus glycoproteins can be used not only to broaden the spectrum of protection against lyssaviruses, but also to express foreign B and CTL epitopes. The potential usefulness of chimeric lyssavirus glycoproteins for the development of multivalent vaccines against animal diseases and zoonoses, including rabies, is discussed.

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(FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
E SCHWARTZ OLIVIER/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

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               E BUSEYNE FLORENCE/IN
L2           1 S E3
L3           0 S L2 NOT L1
               E MARSAC DELPHINE/IN
L4           1 S E3
L5           0 S L4 NOT L1
               E RIVIERE YVES/IN
L6           2 S E3
L7           1 S L6 NOT L1
               E HEARD JEAN MICHEL/IN
L8           6 S E3
L9           5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
               E SCHWARTZ OLIVIER/IN
               E SCHWARTZ O/IN
L10         16 S E3-E5
               E BUSEYNE F/IN
L11          1 S E3
L12          0 S L11 NOT L10
               E MARSAC D/IN
L13          2 S E3
L14          1 S L13 NOT L10
               E RIVIERE Y/IN
L15          7 S E3 OR E4
L16          6 S L15 NOT L10
               E HEARD J/IN
L17          2 S E8
L18          2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
               E SCHWARTZ O/AU
L19         10 S E7
L20         90 S E3
L21          2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
               E BUSEYNE F/AU
L22         25 S E3 OR E4
L23         21 S L22 NOT L20
               E MARSAC E/AU
L24          1 S E2
L25          0 S L24 NOT L20
               E RIVIERE Y/AU
L26        104 S E3 OR E4
L27        101 S L26 NOT L20
               E HEARD J M/AU
L28          7 S E8
L29          7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
               E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30       2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31       1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32        795 S L31 AND EXOGENOUS
L33        790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34         77 S L33 AND PLASMID/CLM
L35         11 S L34 AND PY<2002
L36         49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37        138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38         10 S L37 AND DENDRITIC
L39          1 S L38 AND (GENE VACCINATION)
L40        181 S (NAKED PLASMID DNA)
L41         11 S L40 AND PY=1996
L42          5 S L40 AND DENDRITIC
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L44          80 S MULTIVALENT VACCINE
L45           1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE

=> s multivalen? vaccin?
          2364 MULTIVALEN?
        146418 VACCIN?
L46        162 MULTIVALEN? VACCIN?
                 (MULTIVALEN?(W)VACCIN?)

=> s l46 and (HIV or human immunodeficiency virus)
        136179 HIV
       8499030 HUMAN
        112830 IMMUNODEFICIENCY
        373673 VIRUS
         42682 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L47          6 L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l47,ti,1-6
```

L47 ANSWER 1 OF 6 MEDLINE on STN
TI Generation of multivalent genome-wide T cell responses in HLA-A*0201 transgenic mice by an **HIV**-1 expression library immunization (ELI) vaccine.

L47 ANSWER 2 OF 6 MEDLINE on STN
TI The Children's Vaccine Initiative.

L47 ANSWER 3 OF 6 MEDLINE on STN
TI Recombinant measles viruses expressing heterologous antigens of mumps and simian immunodeficiency viruses.

L47 ANSWER 4 OF 6 MEDLINE on STN
TI Immunogenicity of recombinant envelope glycoproteins derived from T-cell line-adapted isolates or primary **HIV** isolates: a comparative study using **multivalent vaccine** approaches.

L47 ANSWER 5 OF 6 MEDLINE on STN
TI Antibodies from **HIV**-positive and AIDS patients bind to an **HIV** envelope **multivalent vaccine**.

L47 ANSWER 6 OF 6 MEDLINE on STN
TI Recombinant hepatitis B surface antigen as a carrier of **human immunodeficiency virus** epitopes.

=> d l47,cbib,ab,4-6

L47 ANSWER 4 OF 6 MEDLINE on STN
2001317644. PubMed ID: 11391160. Immunogenicity of recombinant envelope glycoproteins derived from T-cell line-adapted isolates or primary **HIV** isolates: a comparative study using **multivalent vaccine** approaches. Lemiale F; Brand D; Lebigot S; Verrier B; Buzelay L; Brunet S; Barin F. (Unite de Virologie, Equipe de Microbiologie Medicale et Moleculaire, Universite Francois Rabelais, Tours, France.) Journal of acquired immune deficiency syndromes (1999), (2001 Apr 15) 26 (5) 413-22. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB We investigated immunogenic properties of native envelope glycoproteins derived from **HIV**-1 (subtype B). Our main objective was to assess whether the design of **multivalent vaccines** affects generation of neutralizing antibodies against primary viruses. Recombinant Semliki Forest virus (SFV) particles producing various **HIV**-1 envelope glycoproteins were used as vaccine vectors. The following **multivalent vaccination** approaches were compared: 1) immunization with a mixture of

HIV-1 primary isolates and two T-cell laboratory-adapted (TCLA) viruses; 2) immunization with a mixture of recombinant SFV expressing only the envelope glycoproteins derived from three **HIV**-1 primary isolates; 3) sequential immunizations with the recombinant SFV expressing the envelope glycoproteins derived from three **HIV**-1 primary isolates and two TCLA viruses, respectively. Two monovalent vaccine approaches using SFV expressing envelope glycoproteins derived from a single primary isolate or TCLA virus were also included in the study. The **multivalent vaccination** strategies based on SFV vaccine vectors did not induce more neutralizing antibodies than the previously tested TCLA envelope immunogens, which gave disappointing results against primary isolates.

L47 ANSWER 5 OF 6 MEDLINE on STN
2000097658. PubMed ID: 10634192. Antibodies from **HIV**-positive and AIDS patients bind to an **HIV** envelope **multivalent vaccine**. Carlos M P; Yamamura Y; Diaz-Mitoma F; Torres J V. (Department of Medical Microbiology and Immunology, School of Medicine, University of California, Davis 95616, USA.) Journal of acquired immune deficiency syndromes (1999), (1999 Dec 1) 22 (4) 317-24. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB A major problem impeding development of an effective **HIV** vaccine is the rapid antigenic variability that is characteristic of several envelope glycoprotein epitopes. Frequent mutations alter the composition of the most immunogenic regions of the envelope glycoprotein. We have prepared a synthetic immunogen representing the evolution of the major hypervariable epitopes on the envelope glycoprotein (gp120) of **HIV**-1. Five synthetic constructs, representing each of the **HIV**-1 gp120 hypervariable epitopes were tested for recognition by antibodies from patients infected with **HIV**-1 from different geographic regions worldwide. An **HIV**-1 human plasma panel provided a representation of the antibodies recognizing subtype-specific epitope sequences prevalent at different parts of the world. The vaccine construct was recognized by antibodies from **HIV**-1-positive individuals infected with subtypes A, B, C, D, E, and F. Antibodies in pooled **HIV**-1 patient sera from San Francisco also recognized all five constructs. This complex immunogen was recognized by antibodies in sera from individual **HIV**-1-positive and AIDS patients from Puerto Rico and Canada, with a strong binding to the complete vaccine and the V3 component. Altogether, our results demonstrate that antibodies from seropositive patients infected with different **HIV**-1 clades recognize and bind to the **HIV** hypervariable epitope construct vaccine preparation and its individual components.

L47 ANSWER 6 OF 6 MEDLINE on STN
94023450. PubMed ID: 7692575. Recombinant hepatitis B surface antigen as a carrier of **human immunodeficiency virus** epitopes. Michel M L; Mancini M; Schlienger K; Tiollais P. (Unite de Recombinaison et Expression genetique, INSERM-U.163, Institut Pasteur, Paris.) Research in virology, (1993 Jul-Aug) 144 (4) 263-7. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Eukaryotic cells transformed with a plasmid expression vector are able to synthesize and assemble HBsAg, a complex multimeric lipoprotein particle. Hybrid particles carrying HIV1 antigenic determinants were constructed and injected into monkeys. A complete immune response including neutralizing antibodies, proliferative and cytotoxic T-cell activities was obtained. Thus, such **HIV**/HBsAg hybrid particles could be a new approach to **multivalent vaccination**.

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     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3
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     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
L28           7 S E8
L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37         138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38          10 S L37 AND DENDRITIC
L39           1 S L38 AND (GENE VACCINATION)
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L41            11 S L40 AND PY=1996
L42             5 S L40 AND DENDRITIC
L43             0 S L40 AND (MULTIVALENT)
L44            80 S MULTIVALENT VACCINE
L45             1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46           162 S MULTIVALEN? VACCIN?
L47             6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l46 and (two plasmids)
       1752296 TWO
         74755 PLASMIDS
           740 TWO PLASMIDS
                 (TWO(W)PLASMIDS)
L48             0 L46 AND (TWO PLASMIDS)

=> d l46,cbib,ab,125-162
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L46 ANSWER 125 OF 162 MEDLINE on STN
93381798. PubMed ID: 8371350. Dengue virus-specific human CD4+ T-lymphocyte responses in a recipient of an experimental live-attenuated dengue virus type 1 vaccine: bulk culture proliferation, clonal analysis, and precursor frequency determination. Green S; Kurane I; Edelman R; Tacket C O; Eckels K H; Vaughn D W; Hoke C H Jr; Ennis F A. (Department of Medicine, University of Massachusetts Medical Center, Worcester 01655.) Journal of virology, (1993 Oct) 67 (10) 5962-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We analyzed the CD4+ T-lymphocyte responses to dengue, West Nile, and yellow fever viruses 4 months after immunization of a volunteer with an experimental live-attenuated dengue virus type 1 vaccine (DEN-1 45AZ5). We examined bulk culture proliferation to noninfectious antigens, determined the precursor frequency of specific CD4+ T cells by limiting dilution, and established and analyzed CD4+ T-cell clones. Bulk culture proliferation was predominantly dengue virus type 1 specific with a lesser degree of cross-reactive responses to other dengue virus serotypes, West Nile virus, and yellow fever virus. Precursor frequency determination by limiting dilution in the presence of noninfectious dengue virus antigens revealed a frequency of antigen-reactive cells of 1 in 1,686 peripheral blood mononuclear cells (PBMC) for dengue virus type 1, 1 in 9,870 PBMC for dengue virus type 3, 1 in 14,053 PBMC for dengue virus type 2, and 1 in 17,690 PBMC for dengue virus type 4. Seventeen CD4+ T-cell clones were then established by using infectious dengue virus type 1 as antigen. Two patterns of dengue virus specificity were found in these clones. Thirteen clones were dengue virus type 1 specific, and four clones recognized both dengue virus types 1 and 3. Analysis of human leukocyte antigen (HLA) restriction revealed that five clones are HLA-DRw52 restricted, one clone is HLA-DP3 restricted, and one clone is HLA-DP4 restricted. These results indicate that in this individual, the CD4+ T-lymphocyte responses to immunization with live-attenuated dengue virus type 1 vaccine are predominantly serotype specific and suggest that a **multivalent vaccine** may be necessary to elicit strong serotype-cross-reactive CD4+ T-lymphocyte responses in such individuals.

L46 ANSWER 126 OF 162 MEDLINE on STN
93317401. PubMed ID: 8327313. Pediatric experience with recombinant hepatitis B vaccines and relevant safety and immunogenicity studies. Greenberg D P. (UCLA School of Medicine, Harbor-UCLA Medical Center, Torrance 90502.) Pediatric infectious disease journal, (1993 May) 12 (5) 438-45. Ref: 73. Journal code: 8701858. ISSN: 0891-3668. Pub. country: United States. Language: English.

AB Yeast-derived recombinant hepatitis B vaccines have replaced plasma-derived vaccines in the United States and have now been given to millions of infants and children throughout the world. Routine immunization of infants in the United States with hepatitis B vaccine has been endorsed as the optimal means to prevent infection. The recombinant vaccines have an excellent safety record; most children have no adverse

that resolve within a short time. Both of the vaccines licensed in the United States are highly immunogenic in infants and children who complete a three dose vaccination sequence. Approximately 95 to 100% achieve protective levels of antibody to hepatitis B surface antigen (> or = 10 mIU/ml) after three doses. Immunization may begin at birth or at 1 to 2 months of age, and hepatitis B vaccine may be given simultaneously with other routine childhood vaccines. Antibody levels to hepatitis B surface antigen gradually wane over time, and the duration of maintaining protective levels correlates strongly with the peak level achieved. The protective efficacy against perinatal transmission from mothers who are positive for hepatitis B surface antigen and e antigen is 90 to 100% when the first dose of vaccine is administered at birth with hepatitis B immunoglobulin. In highly endemic populations immunization in infancy also protects against horizontal transmission from chronically infected family members. Studies currently in progress will determine the duration of protection, the potential need for booster doses and the feasibility of combining antigens in **multivalent vaccines**.

L46 ANSWER 127 OF 162 MEDLINE on STN
93263855. PubMed ID: 8098601. The effects of antigenic competition on the efficacy of multivalent footrot vaccines. Schwartzkoff C L; Egerton J R; Stewart D J; Lehrbach P R; Elleman T C; Hoyne P A. (Arthur Webster Pty Ltd., Baulkham Hills, New South Wales.) Australian veterinary journal, (1993 Apr) 70 (4) 123-6. Journal code: 0370616. ISSN: 0005-0423. Pub. country: Australia. Language: English.

AB A multivalent footrot vaccine has been developed, containing pilus antigens produced in recombinant Pseudomonas aeruginosa and representing all nine serogroups of Dichelobacter (Bacteroides) nodosus commonly recognised in the field. The responses of sheep to the **multivalent vaccine** have been compared with those to monovalent vaccines representing only a single serogroup. Antigenic competition between serogroups occurred in sheep immunised with the multivalent formation, but high levels of protection were still achieved. The study showed that in multivalent footrot vaccines, antigenic competition is predominantly due to the presence of a family of immunologically-related pilus antigens rather than to interference by extraneous proteins.

L46 ANSWER 128 OF 162 MEDLINE on STN
93110969. PubMed ID: 1335196. Current status and prospects of live varicella vaccine. Takahashi M. (Research Institute for Microbial Diseases, Osaka University, Japan.) Vaccine, (1992) 10 (14) 1007-14. Ref: 73. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Since its development in 1974 the Oka strain live attenuated varicella vaccine has been tested in healthy and immunocompromised adults and children. Its safety and efficacy have been established and it is now licensed for general use in Japan and Korea, and for immunocompromised patients in several other countries. Possibilities for the future include its use to prevent zoster in the elderly, its incorporation in a **multivalent vaccine** and its use as a vehicle to express foreign genes in recombinant vaccines.

L46 ANSWER 129 OF 162 MEDLINE on STN
93107844. PubMed ID: 1469350. Strain-specific selection of genome segments in avian reovirus coinfections. Ni Y; Kemp M C. (Department of Veterinary Pathobiology, College of Veterinary Medicine, Texas A&M University, College Station 77843.) Journal of general virology, (1992 Dec) 73 (Pt 12) 3107-13. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB To determine whether selection of genome segments in coinfections is strain-specific, chicken embryo fibroblasts were coinfected with avian reovirus strain 883 and one of three other avian reovirus strains (176, S1133 and 81-5). Viral progeny from each coinfection (883 x 176, 883 x S1133 or 883 x 81-5) was serially passaged at a low m.o.i. The electropherotypes of the coinfection progeny and those of the

plaque derived clones obtained from passages 1 and 20 were analysed. Two 883 segments (M2 and S2) were found to be selected in the 883 x 176 coinfection, three 883 segments (M2, M3 and S2) in the 883 x S1133 coinfection, and only one 883 segment (M3) in the 883 x 81-5 coinfection, i.e. different 883 genome segments were selected in the three coinfections. It was, therefore, concluded that selection of genome segments in a coinfection of a given cell line is virus strain-specific. The selection of genome segments in coinfections was shown to be due to enhanced infectivity of the reassortants that were formed in the coinfections. In addition, defective interfering particles that lack the S1 segment were identified in the 883 x 81-5 coinfection progeny following serial passage. Selection of genome segment(s) in coinfections as described herein may have potential importance on the effect and production of divalent or **multivalent vaccines**.

L46 ANSWER 130 OF 162 MEDLINE on STN

93026649. PubMed ID: 1668679. Multiple antigen peptides (MAPs) as candidate vaccines against malaria. Pessi A; Bianchi E; Chiappinelli L; Bonelli F; Tougne C; Lambert P H; Del Giudice G. (Peptide Synthesis Unit, SCLAVO SpA, Monterotondo, Rome, Italy.) Parassitologia, (1991 Apr) 33 (1) 79-84. Journal code: 0413724. ISSN: 0048-2951. Pub. country: Italy. Language: English.

AB Multiple Antigen Peptides (MAPs), branched molecules where multiple copies of a desired antigenic sequence are assembled on a small peptide core, have been recently described as an alternative approach to the synthesis of high molecular weight immunogens. In comparison with conventional peptide-carrier conjugates, the MAPs show several advantages, including chemical unambiguity and ease of synthesis. A MAP based on the sequence of the repetitive domain of P. malariae sporozoites was immunogenic in a large number of mouse strains. When covalently linked to the corresponding sequence of the P. falciparum circumsporozoite protein, [NANP]40, the resulting conjugate showed the properties of a **multivalent vaccine**, overcoming the severe genetic restriction of the [NANP] sequence. A second generation of MAPs including both sequences, with more desirable chemical properties, was equally effective. These compounds represent a promising step towards the development of synthetic, multivalent peptide vaccines against human malaria.

L46 ANSWER 131 OF 162 MEDLINE on STN

92387988. PubMed ID: 1517133. Effects of vaccination against 18 immunogens in beef replacement heifers at weaning. Carmel D K; Barao S M; Douglass L W. (Department of Veterinary Medicine, Virginia-Maryland Regional College of Veterinary Medicine, College Park.) Journal of the American Veterinary Medical Association, (1992 Aug 15) 201 (4) 587-90. Journal code: 7503067. ISSN: 0003-1488. Pub. country: United States. Language: English.

AB Humoral immune responses to vaccination, mean daily body-weight gains, morbidity, and mortality were compared in groups of beef replacement heifers from weaning to 4 months after weaning. The only difference in management among groups of heifers was the number and type of vaccines they received. Heifers were vaccinated at weaning (mean age, 205 days) and again 28 days later against 0, 1, 9, 10, 17, or 18 antigens, using commercially available monovalent and **multivalent vaccines**. The common vaccine component in all treatment groups was a modified-live bovine respiratory syncytial virus. Mean daily gain, morbidity, mortality, and serum neutralization antibody titers to bovine respiratory syncytial virus did not differ among treatment groups. Although the study revealed the safety of vaccinating beef heifers against 18 antigens at weaning, our data emphasized the need for serial vaccination to induce a measurable serum antibody response.

L46 ANSWER 132 OF 162 MEDLINE on STN

92387329. PubMed ID: 1516666. Fasciola hepatica: host responders and nonresponders to parasite glutathione S-transferase. Hillyer G V; Soler de Galanes M; Battisti G. (Department of Pathology, University of Puerto Rico, School of Medicine, San Juan 00936-5067.) Experimental parasitology, (1992 Sep) 75 (2) 176-86. Journal code: 0370713. ISSN:

0014-4894. Pub. country: United States. Language: English.
AB Fasciola hepatica glutathione S-transferase (FhGST) was isolated from adult worms by glutathione agarose affinity chromatography. SDS-PAGE shows three proteins of M(r) ranging from 29-27.8 kDa. Western immunoblot analyses using SDS-PAGE separated adult worm extracts and probed with a rabbit anti-FhGST antiserum reveal two bands in the same M(r) range. Mice and rabbits immunized with purified FhGST develop copious amounts of anti-FhGST antibodies. Moreover, antisera to F. hepatica adult worms and excretion-secretion products also react with FhGST. Cross-reactivity with schistosomes is evidenced in the reactivity with FhGST of anti-Schistosoma mansoni adult worm antisera and, to a lesser extent, antisera to S. mansoni-soluble egg antigens. The time of appearance of anti-FhGST antibodies in different species of animals infected with F. hepatica was determined. Sheep and a New Zealand white rabbit developed anti-FhGST antibodies detectable by ELISA as early as 2 weeks postexposure with F. hepatica. However, neither mice nor calves infected with F. hepatica developed antibodies to FhGST through the 5-10 weeks of infection tested. But mice infected with S. mansoni developed anti-FhGST cross-reacting antibodies by 6 weeks of infection. Calves immunized with a Fasciola/Schistosoma cross-reactive, cross-protective antigen complex in which a 12,000-kDa protein (Fh12) has been shown to contain immunoprophylactic activity, also developed antibodies to FhGST. Since FhGST is a novel potential vaccine, its protection-inducing capability in a **multivalent vaccine** combined with Fh12 clearly warrants study. In summary, it appears that hosts with fascioliasis are either responders to FhGST (rabbits, sheep) or nonresponders (mice, cattle), offering interesting models for studying the immune response.

L46 ANSWER 133 OF 162 MEDLINE on STN
92372423. PubMed ID: 1506249. Colostral transfer of Bacteroides nodosus antibodies in sheep. Bartram P A; Glenn J S; Lasslo L L. (Department of Reproduction, School of Veterinary Medicine, University of California, Davis 95616.) Journal of the American Veterinary Medical Association, (1992 Aug 1) 201 (3) 445-8. Journal code: 7503067. ISSN: 0003-1488. Pub. country: United States. Language: English.
AB Ovine contagious foot rot may cause lameness in sheep, resulting in decreased wool growth and low weight gain. Affected neonatal lambs are difficult to treat, and treatment is labor intensive; thus, a method of prevention is warranted. Vaccination of ewes with a **multivalent vaccine** in an oil adjuvant induced development of antibody to the somatic O antigen of Bacteroides nodosus, and this antibody was detected in serum of newborn lambs after consumption of colostrum from the vaccinated ewes. Antibody titers were determined in 48 unvaccinated ewe/lamb pairs, and in 50 once-vaccinated and 78 twice-vaccinated pairs. Serum and colostrum O-agglutinin titers to B nodosus were determined by a microtitration agglutination test. Lambs from vaccinated ewes had significantly (P less than 0.05) higher O-agglutinin titers than those from unvaccinated ewes, and double vaccination of ewes resulted in the highest potentially protective titers (greater than 1:2,400) in ewes and lambs.

L46 ANSWER 134 OF 162 MEDLINE on STN
92347986. PubMed ID: 1639486. Construction of a multivalent meningococcal vaccine strain based on the class 1 outer membrane protein. Van Der Ley P; Poolman J T. (National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.) Infection and immunity, (1992 Aug) 60 (8) 3156-61. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.
AB Outer membrane complexes (OMCs) are promising vaccine candidates for protection against meningococcal disease. However, a major obstacle to this approach is the fact that the protective antibodies induced are generally type specific. In an attempt to overcome this problem, we have investigated the possibility of constructing a **multivalent vaccine** strain by insertion of an additional class 1 outer membrane protein-encoding gene. Starting with a derivative of strain H44/76 deficient in class 3 outer membrane protein, a second class 1 gene was

inserted into the chromosome, through homologous recombination with a suicide plasmid carrying the class 1 gene from strain 2996 placed within a class 5 gene. In this way, a strain was obtained in which a class 3 protein was in effect replaced by a class 1 protein from another subtype, i.e. P1.5,2 in addition to the P1.7,16 protein of H44/76. Immunization of mice with such OMCs resulted in high bactericidal titers against both H44/76 and 2996, where normally only strain-specific antibodies are induced. Mutational removal of class 3 protein from the immunizing OMCs had no detectable effect on the bactericidal titer against H44/76, whereas removal of class 1 protein led to a strong reduction. These results demonstrate the dominant role of the subtype-specific sequences of class 1 protein in the induction of bactericidal antibodies and show that construction of a multivalent OMC-based vaccine should be feasible.

L46 ANSWER 135 OF 162 MEDLINE on STN
92320086. PubMed ID: 1352408. Humoral responses to a **multivalent vaccine** in age-matched lambs of different bodyweight and nutrition. Whittington R J; Edwards S R; Nicholls P J; Neutze S A; Oddy V H; Farrugia J A; Egerton J R. (Elizabeth Macarthur Agricultural Institute, Camden, New South Wales, Australia.) Research in veterinary science, (1992 May) 52 (3) 277-83. Journal code: 0401300. ISSN: 0034-5288. Pub. country: ENGLAND: United Kingdom. Language: English.

AB K-agglutination, pilus-enzyme-linked immunosorbent assay (ELISA) and outer membrane protein-ELISAs were used to assess humoral responses after vaccination with a commercial, multivalent, ovine foot rot vaccine (Dichelobacter nodosus whole cells) in three groups of nine-month-old lambs of markedly different bodyweight, nutritional history and dietary protein supply. Mean bodyweights of lambs in low (L), medium (M) and high (H) bodyweight/nutrition groups were 22, 32 and 48 kg, respectively, at the time of vaccination. Few significant differences in humoral responses to vaccine antigens were found between groups. However, lambs in group H tended to have lower levels of antibody to a greater number of component antigens than did lambs in the other groups. These results suggest that low bodyweight due to poor nutrition is unlikely to affect the response of sheep to multivalent foot rot vaccines.

L46 ANSWER 136 OF 162 MEDLINE on STN
92267544. PubMed ID: 1587542. Vaccination against acute respiratory virus infections and measles in man. Osterhaus A D; de Vries P. (Laboratory of Immunobiology, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.) Immunobiology, (1992 Feb) 184 (2-3) 180-92. Ref: 37. Journal code: 8002742. ISSN: 0171-2985. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Several viruses may cause more or less severe acute respiratory infections in man, some of which are followed by systemic infection. Only for influenza and measles are licensed vaccines available at present. The protection induced by influenza vaccines, which are based on inactivated whole virus or viral subunits, depends largely on the matching of vaccine strain and circulating virus. Measles vaccines, which are based on attenuated live virus, have been quite effective in controlling the disease in vaccinated populations in the industrialized world. In developing countries, severe measles infections occur in infants from six to nine months of age, which necessitates the vaccination of children of less than six months. At that time maternal antibodies, that may interfere with the induction of protection, may still be present. Therefore, instead of using the parenteral route, the possibility to use the mucosal route of primary immunization is also investigated for vaccination with attenuated live measles vaccines. The use of inactivated measles vaccines has resulted in a state of immunity which upon exposure to the virus may induce an atypical measles syndrome including a severe pneumonia. Measles virus proteins presented in an iscom matrix have recently been shown to induce functional B and T cell responses to both the surface glycoproteins of the virus. These responses could also be induced in the presence of virus neutralizing antibodies and they proved to be protective in several animal model systems. Many of the problems that have been encountered in the development of measles vaccines, proved

causing acute respiratory infections in man, including respiratory syncytial virus. Parenteral application of inactivated and attenuated live vaccines against these paramyxoviruses has generally had little success. Topical application of attenuated live vaccines has been more successful, and also the use of vaccinia recombinant viruses expressing foreign paramyxoviral glycoproteins has shown promising results in laboratory animals. Live vaccines based on adenovirus types 4 and 7 in oral enteric-coated vaccines, which lead to virus replication in the intestines but not in the respiratory tract have been included in military vaccination programs. The possibility to replace e.g. the E3 region with foreign DNA makes adenoviruses also suitable as cloning vectors for proteins of other respiratory viruses. Although live attenuated vaccines against some of the serotypes of rhinoviruses have shown promising results, the generation of a **multivalent vaccine** against this epidemiologically most significant cause of acute respiratory infections will be almost impossible, due to the multiplicity of serotypes involved.(ABSTRACT TRUNCATED AT 400 WORDS)

L46 ANSWER 137 OF 162 MEDLINE on STN

91243284. PubMed ID: 1709836. Evidence implicating MHC genes in the immunological nonresponsiveness to the Plasmodium falciparum CS protein. Good M F; Kumar S; De Groot A S; Weiss W R; Quakyi I A; Dontfraid F; Smith G E; Cochran M; Berzofsky J A; Miller L H. (Laboratory of Parasitic Diseases, N.I.A.I.D., National Institutes of Health, Bethesda, MD.) Bulletin of the World Health Organization, (1990) 68 Suppl 80-4. Journal code: 7507052. ISSN: 0042-9686. Pub. country: Switzerland. Language: English.

AB The circumsporozoite (CS) protein is a major candidate vaccine antigen for the sporozoite stage of malaria. Both cytotoxic T cells (CTL) and antibody specific for the CS protein are thought to be important in protection. By examining the immune response in mice and humans we have shown that genes mapping to the major histocompatibility complex (MHC) are important for immune responsiveness. F1 mice between high antibody responders and low antibody responders are high antibody responders, suggesting that in this model immune suppressor genes do not control the immune response. Using synthetic peptides to map epitopes for CTL and helper T cells (which are important for the antibody response) we have shown that the T-cell epitopes are located in the polymorphic region of the protein, and we hypothesize that T cells have indeed selected the variation observed in the CS protein. The success of subunit vaccines will depend on the pattern of variation in different geographical locations, the ability to construct **multivalent vaccines** containing different variant epitopes from this protein, and on the existence of other sporozoite and liver-stage proteins involved in protection.

L46 ANSWER 138 OF 162 MEDLINE on STN

90347214. PubMed ID: 2143519. Secondary structure and immunogenicity of hybrid synthetic peptides derived from two Plasmodium falciparum pre-erythrocytic antigens. Londono J A; Gras-Masse H; Dubeaux C; Tartar A; Druilhe P. (Laboratoire de Parasitologie Medicale, Institut Pasteur, Paris, France.) Journal of immunology (Baltimore, Md. : 1950), (1990 Sep 1) 145 (5) 1557-63. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Multicomponent synthetic vaccines containing both B and T cell epitopes belonging to two different pre-erythrocytic Ag of Plasmodium falciparum are presented. In a di-component hybrid, a circumsporozoite T cell epitope and a peptide representing a liver stage-specific Ag were connected to obtain a reciprocal reinforcement of helical potentials. In a tri-component hybrid, a sequence corresponding to the circumsporozoite repeat tetrapeptide (NPNA) was tandemly synthesized on the N-terminal end of the di-component hybrid. Both hybrid molecules were able to adopt a partial helical conformation in water as determined by circular dichroism studies. To analyze if the different components were immunologically functional in these vaccines, mich bearing genetic backgrounds known to respond or not to the individual components were immunized with the

hybrids. The tri-hybrid peptide showed high immunogenic capacity, as it elicited, in both H-2b and H-2k mice, high antibody responses against every separate individual sequence. Moreover, the antibodies induced by these conformationally restricted peptides were able to recognize the corresponding native proteins in the liver schizont and the sporozoite surface. H-2d mice, in which the immune response to the individual components was genetically restricted, did respond against the di-hybrid peptide. The tri-hybrid peptide, in which NPNA repeats were present, lacked this H-2d-priming capacity but it triggered antibody production in H-2d mice previously primed with the di-hybrid peptide. These results indicate that **multivalent vaccines** can provide positive (potentiating) effects by carefully combining structurally well defined epitopes; however, negative (suppressive) effects are also possible suggesting that selection of **multivalent vaccine** components will require testing of combined molecules to optimize specific immune responses and avoid undesirable effects which may result from negative molecular interactions.

L46 ANSWER 139 OF 162 MEDLINE on STN
90334344. PubMed ID: 2378463. Antigenic structure of Coxiella burnetii. A comparison of lipopolysaccharide and protein antigens as vaccines against Q fever. Williams J C; Hoover T A; Waag D M; Banerjee-Bhatnagar N; Bolt C R; Scott G H. (United States Army Medical Research Institute of Infectious Diseases, Department of Intracellular Pathogens, Fort Detrick, Frederick, Maryland 21701-5011.) Annals of the New York Academy of Sciences, (1990) 590 370-80. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The antigenic structure of Coxiella burnetii is being investigated by identifying both external and internal cellular epitopes of the morphologic cell types. Both the phase I lipopolysaccharide (LPSI) and several surface proteins are candidates for the development of subunit **multivalent vaccines**. The protective efficacy of purified LPSI was demonstrated in A/J mice. The purified LPSI preparations contained residual peptides detected by amino acid analysis. Therefore, the protection afforded by LPSI may be, in part, due to the presence of peptides. The purification of proteins free of LPSI must be accomplished before the protective efficacy of proteins or peptides can be established. We have identified three proteins that are both antigenic and immunogenic, as indicated by either enzyme immunoassay, radioimmunoprecipitation, immunoblot assay, or lymphocyte transformation. A 62-kDa protein antigen encoded by the htpB gene of C. burnetii was analyzed for immunogenicity. The purified protein antigen was immunogenic, as it elicited specific antibodies and performed as recall antigen in lymphocyte stimulation assays. The antigen was not detected on the surface of phase I cells but was highly represented on the surface of phase II cells. Therefore, the protein may not be a good candidate for vaccine development. The diagnostic utility of the 62-kDa protein antigen lies in the fact that convalescent and chronic Q fever sera from human patients reacted with the antigen, whereas acute sera did not. Although the 62-kDa protein is a "common antigen," specific peptide-based diagnostic reagents may be useful in the detection of Q fever disease progression. A major surface protein (P1) of roughly 29.5 kDa was purified from the phase I Nine Mile (clone 7) strain. No LPSI was detected in the P1 preparation by three different LPSI monoclonal antibodies. Monoclonal antibodies prepared against P1 were effective in localizing the protein on the cell surface, in the cell wall, and associated with the peptidoglycan of large cells of C. burnetii. Small, pressure-resistant cells did not contain P1. Mice immunized with two 25-micrograms injections of LPSI produced antibodies against LPSI and phase I whole cells. No antibody was detected against phase II whole cells. Immunization with P1 induced antibody against the LPSI fraction and phase I and phase II whole cells. P1 was more effective than LPSI in reducing the number of infectious C. burnetii in the spleens of challenged mice. The gene encoding another protein (P2) recognized by P1 monoclonal antibodies was cloned and sequenced.(ABSTRACT TRUNCATED AT 400 WORDS)

L46 ANSWER 140 OF 162 MEDLINE on STN
90312827. PubMed ID: 2142352. Inactivated canine parvovirus vaccines: an

alternative method for assessment of potency. Goddard R D; Nicholas R A; Luff P R. (Central Veterinary Laboratory, New Haw, Weybridge, Surrey.) Veterinary record, (1990 May 19) 126 (20) 497-9. Journal code: 0031164. ISSN: 0042-4900. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Groups of three-week-old chickens were given graded doses of inactivated canine parvovirus vaccines. Blood samples were taken three weeks later and the sera examined by ELISA for antibodies to canine parvovirus. Reproducible, linear, log-dose serological responses were observed, enabling the potency of the vaccines to be compared. The simultaneous administration of other components of canine **multivalent vaccines** appeared to reduce the response to the parvovirus component. When its results have been correlated with the degree of protection in dogs this test could be used to assess the potency of inactivated canine parvovirus vaccines.

L46 ANSWER 141 OF 162 MEDLINE on STN

90118299. PubMed ID: 2481908. Live Salmonella as vaccines and carriers of foreign antigenic determinants. Chatfield S N; Strugnell R A; Dougan G. (Department of Molecular Biology, Wellcome Research Laboratories, Beckenham, Kent, UK.) Vaccine, (1989 Dec) 7 (6) 495-8. Ref: 47. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Salmonella species can be rationally attenuated by introducing non-reverting defined mutations into the genome to produce live vaccine strains. Several genes have been identified which when mutated, will attenuate Salmonellae. In particular, salmonella strains harbouring mutations in genes involved in the pre-chorismate biosynthetic pathway make excellent oral vaccines evoking strong humoral, local and cellular immune responses in the host. Because of the spectrum of immune responses induced by live vaccine strains they have the potential to be used for delivery of heterologous antigens to the mammalian immune system. A number of antigens from other bacteria, viruses and parasites have been expressed in live salmonella vaccine strains. Such hybrid strains have the potential to be used as **multivalent vaccines** against a number of infectious diseases.

L46 ANSWER 142 OF 162 MEDLINE on STN

90077969. PubMed ID: 2687219. Animal health research in the Small Ruminant Collaborative Research Support Program. Alexander A F; DeMartini J C; McGuire T C; Olander H J. (Dept. of Pathol., College of Vet. Med. and Biomed. Sci., Colorado State University, Fort Collins 80523.) Journal of animal science, (1989 Nov) 67 (11) 3103-10. Ref: 23. Journal code: 8003002. ISSN: 0021-8812. Pub. country: United States. Language: English.

AB Disease is a major constraint in small ruminant production systems in lesser-developed countries throughout the world. Animal health projects have been an integral part of the Small Ruminant Collaborative Research Support Program (SR-CRSP) from its inception. At the onset, these projects were oriented toward herd health care and veterinary extension activities. Later, all the projects developed a sharper focus in that they were directed to more basic studies of infectious disease. Diseases currently being investigated include caseous lymphadenitis, contagious caprine pleuropneumonia, caprine arthritis-encephalitis, ovine pulmonary carcinoma, ovine progressive pneumonia and neonatal mortality of alpaca. Continued, sharply focused studies are projected for the future to take advantage of recombinant technology in the development of **multivalent vaccines**.

L46 ANSWER 143 OF 162 MEDLINE on STN

90043872. PubMed ID: 2509909. Specificities of antibodies that inhibit merozoite dispersal from malaria-infected erythrocytes. Lyon J A; Thomas A W; Hall T; Chulay J D. (Department of Immunology, Walter Reed Army Institute of Research, Washington, DC 20307-5100.) Molecular and biochemical parasitology, (1989 Aug) 36 (1) 77-85. Journal code: 8006324. ISSN: 0166-6851. Pub. country: Netherlands. Language: English.

AB When malaria schizont-infected erythrocytes are cultured with immune serum, antibodies prevent dispersal of merozoites, resulting in the

formation of immune clusters of merozoites (ICM) and inhibition of parasite growth. Antigens recognized by these antibodies were identified by probing two dimensional immunoblots of Plasmodium falciparum antigens with antibodies dissociated from immune complexes present at the surface of merozoites in ICM. Total immune serum recognized 88 of the 135 protein spots detected by colloidal gold staining, but antibodies dissociated from immune complexes recognized only 15 protein spots attributable to no more than eight distinct antigens. Antigens recognized by antibodies that inhibit merozoite dispersal include the precursor to the major merozoite surface antigens (gp195), a 126-kDa serine-repeat antigen (SERA), the 130-kDa protein that appears to bind to glycophorin (GBP130), and the approx. 45-kDa merozoite surface antigen. One other antigen (230/215-kDa doublet) was identified by using antibodies affinity purified from recombinant expression proteins. The identities of the other three antigens (150 kDa, 127 kDa and less than 30 kDa) were not determined. This approach provides a strategy for identifying epitopes accessible at the merozoite surface which may be important components of a **multivalent vaccine** against blood stages of P. falciparum.

L46 ANSWER 144 OF 162 MEDLINE on STN
90026773. PubMed ID: 2679630. Solid matrix-antibody-antigen (SMAA) complexes for constructing multivalent subunit vaccines. Randall R E. Immunology today, (1989 Oct) 10 (10) 336-9. Ref: 25. Journal code: 8008346. ISSN: 0167-5699. Pub. country: ENGLAND: United Kingdom. Language: English.

AB For successful vaccination to many diseases, it is necessary to induce both humoral and cell-mediated immune responses to the infectious agent: this may require the incorporation of multiple antigens from the same microbe into the vaccine. In this article, Richard Randall proposes that one of the most practical and effective ways of producing **multivalent vaccines** may be through the construction of solid matrix-antibody-antigen (SMAA) complexes. The advantages of such vaccines and their future potential is discussed.

L46 ANSWER 145 OF 162 MEDLINE on STN
89388968. PubMed ID: 3151530. Sensitization against the parasite antigen Sj26 is not sufficient for consistent expression of resistance to Schistosoma japonicum in mice. Mitchell G F; Garcia E G; Davern K M; Tiu W U; Smith D B. (Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia.) Transactions of the Royal Society of Tropical Medicine and Hygiene, (1988) 82 (6) 885-9. Journal code: 7506129. ISSN: 0035-9203. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mice immunized with purified antigen preparations produced in Escherichia coli and containing the glutathione S-transferase (GST) isoenzyme of Schistosoma japonicum (Sj26) can be partially resistant to infection with this parasite. Maximum resistance was approximately 50% and no protection was obtained in BALB/c mice, known low responders to Sj26. Although only Freund's complete adjuvant has been used, the data obtained indicate that satisfactory levels of resistance to S. japonicum will not be attained by vaccination with Sj26 alone. Other antigens, including the additional GST isoenzyme of S. japonicum Sj28, will probably be required to establish whether Sj26 will be an important component of a defined **multivalent vaccine** against schistosomiasis japonica.

L46 ANSWER 146 OF 162 MEDLINE on STN
89346552. PubMed ID: 2548276. Prospects for development of a rotavirus vaccine against rotavirus diarrhea in infants and young children. Kapikian A Z; Flores J; Hoshino Y; Midthun K; Gorziglia M; Green K Y; Chanock R M; Potash L; Sears S D; Clements M L; +. (Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892.) Reviews of infectious diseases, (1989 May-Jun) 11 Suppl 3 S539-46. Ref: 49. Journal code: 7905878. ISSN: 0162-0886. Report No.: PIP-060749; POP-00224290. Pub. country: United States. Language: English.

AB Major advances have been made in elucidating the etiologic agents of

severe infantile diarrhea, and it is clear that rotaviruses are the single most important etiologic agents. Progress in the development of rotavirus vaccine candidates has also moved swiftly with the "Jennerian" approach, in which a related live, attenuated rotavirus strain from a nonhuman host is used as the immunizing antigen. If this strategy is not effective against all rotavirus serotypes, reassortant rotaviruses hold great promise for the development of a **multivalent vaccine**. Field trials with the "Jennerian" approach vaccines are under way, and phase 1 trials with the reassortants have been initiated. In 1972, the 27-nm Norwalk virus associated with epidemic viral gastroenteritis in older children and adults was discovered, and in 1973, the detection of the 70-nm human rotavirus associated with acute gastroenteritis in infants and young children followed. They are responsible for 35-50% of severe diarrhea in children under 2. In a Bangladesh study, rotaviruses were the most frequent pathogens in children under 2 with diarrheal illnesses. 4 epidemiologically important human rotavirus serotypes have been identified. After inoculation in utero with bovine rotavirus (NCDV), calves were protected against disease following challenge at birth with human rotavirus type 1. The human rotavirus vaccine, RIT 4237, is derived from the cold-adapted bovine rotavirus NCDV (Lincoln) strain. A single oral dose of the vaccine provided a protection rate of 88% against rotavirus diarrhea in 178 Finnish infants 8-11 months of age. An 82% protection rate was observed in 331 Finnish infants 6-12 months of age following 2 oral doses. The rhesus rotavirus strain MMU 18006 as a candidate rotavirus vaccine was safe and antigenic after oral administration in adult volunteers, children, and infants. The rhesus rotavirus vaccine induced significant febrile reactions in 64% and watery stools in 20% of 608 month old Finnish infants; and it was more antigenic than the RIT 4237 vaccine. Neither adult volunteers became ill during recent phase 1 trials in Baltimore with 2 rotaviruses: the D (human rotavirus serotype 1) x RRV (rhesus rotavirus) reassortant. Similar studies were carried out with a DS-1 x RRV reassortant in 2 volunteers with high levels of prechallenge plaque-reduction neutralization (PRN) antibody to this reassortant. Neither volunteer became ill. Later 14 volunteers with little prechallenge PRN serum antibody to this reassortant were given the reassortant; none developed diarrheal illness. Each of the 4 rotavirus serotypes has been isolated from newborns with asymptomatic infections 1 strain recovered from asymptomatic neonates within the first 14 days of life induced significant protection against serious rotavirus disease for up to 3 years. Attenuation of virulent human rotavirus strain might also be achieved by cold adaptation.

L46 ANSWER 147 OF 162 MEDLINE on STN

89339722. PubMed ID: 2569448. Cross-reactivity of Pseudomonas aeruginosa antipilin monoclonal antibodies with heterogeneous strains of P. aeruginosa and Pseudomonas cepacia. Saiman L; Sadoff J; Prince A. (Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York 10032.) Infection and immunity, (1989 Sep) 57 (9) 2764-70. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB Much of the morbidity and mortality in patients with cystic fibrosis (CF) is secondary to pulmonary infections with Pseudomonas aeruginosa and, more recently, with Pseudomonas cepacia. Prevention of colonization and subsequent infection would be a useful therapeutic strategy. The pili (fimbriae) of P. aeruginosa are a potential vaccine antigen, as they have been implicated in binding to respiratory epithelium and appear to have limited antigenic diversity. Monoclonal antibodies (MAbs) raised to P. aeruginosa pilin demonstrated significant cross-reactivity, as four of five P. aeruginosa strains with known pilin sequences and 10 of 15 P. aeruginosa clinical isolates hybridized by immunoblot with at least one of the three MAbs tested. The P. cepacia strains demonstrated minimal cross-reactivity with these MAbs, as only 2 of 16 strains hybridized immunologically. The three MAbs decreased the adherence of 35S-labeled P. aeruginosa PA1244 to bovine tracheal cells by 56, 45, and 31%. One of these MAbs decreased the adherence of strains P. aeruginosa PAO1 and P. cepacia 249 to CF epithelial cells by 46 and 25%, respectively. While

with CF, these studies give support for a **multivalent vaccine** strategy using P. aeruginosa pilin as the immunogen.

L46 ANSWER 148 OF 162 MEDLINE on STN

89254760. PubMed ID: 2542202. Efficacy of viral components of a nonabortigenic combination vaccine for prevention of respiratory and reproductive system diseases in cattle. Talens L T; Beckenhauer W H; Thurber E T; Cooley A J; Schultz R D. (Biological Research and Development Division, Norden Laboratories, Lincoln, NE 68501.) Journal of the American Veterinary Medical Association, (1989 May 1) 194 (9) 1273-80. Journal code: 7503067. ISSN: 0003-1488. Pub. country: United States. Language: English.

AB Efficacy and safety of components of an IM-administered vaccine for prevention of infectious bovine rhinotracheitis virus (IBRV), parainfluenza type-3 (PI-3) virus, bovine viral diarrhea virus (BVDV), and respiratory syncytial virus (RSV) infections and campylobacteriosis and leptospirosis were evaluated in cattle, including calves and pregnant cows. Challenge of immunity tests were conducted in calves for IBRV, PI-3 virus, or BVDV vaccinal components. All inoculated calves developed serum-neutralizing antibodies and had substantially greater protection (as measured by clinical rating systems) than did controls after challenge exposure to virulent strains of IBRV, PI-3 virus, BVDV, or RSV. In in utero tests, IBRV or bovine RSV vaccinal strains were inoculated into fetuses of pregnant cows. Histologic changes or abortions did not occur after fetal inoculation of the RSV vaccinal strain, and 10 of 14 fetuses responded serologically. Of 9 fetuses, one responded serologically to the IBRV vaccinal strain after in utero inoculation and was aborted 3 weeks later. In an immunologic interference test, 10 calves vaccinated with 2 doses of the **multivalent vaccine**, containing the 4 viral components and a Campylobacter-Leptospira bacterin, developed serum-neutralizing antibodies to IBRV, PI-3 virus, BVDV, and RSV without evidence of serologic interference. Under field conditions, 10,771 cattle, including 4,543 pregnant cows, were vaccinated. Vaccine-related abortions did not occur.

L46 ANSWER 149 OF 162 MEDLINE on STN

89114482. PubMed ID: 2851184. The present status of rotavirus vaccine development. Bishop R. (Department of Gastroenterology, Royal Children's Hospital, Melbourne, Victoria, Australia.) Southeast Asian journal of tropical medicine and public health, (1988 Sep) 19 (3) 429-35. Journal code: 0266303. ISSN: 0125-1562. Pub. country: Thailand. Language: English.

AB Rotavirus infection is one of the most important causes of morbidity in young children throughout the world. The high associated mortality in Southeast Asia (and elsewhere) warrants the development of a vaccine. It is probable that most of the life-threatening watery diarrhoea due to rotavirus infection occurs as a result of primary infection in children aged 6-18 months after protection due to maternal antibody has diminished. Thus rotavirus vaccines are targeted at young infants from birth to 3 months of age. At present three candidate rotavirus vaccines (RIT-4237, MMU-18007, WC3) have undergone trials in young children. A bovine rotavirus strain (RIT-4237), was shown to be safe, immunogenic and efficacious in prevention of severe rotavirus diarrhoea in young children in Finland. However it was found to be weakly immunogenic in infants in developing countries, and to have only low efficacy in prevention of disease. A simian rotavirus strain (RRV, MMU-18006) has proved to be highly immunogenic and its reactinogenicity to be diminished by pre-existing maternal antibody (in infants aged 1-4 months). It has high efficacy against clinically severe rotavirus infection. However protection is homotypic against human serotype 3 only so that eventually a **multivalent vaccine** incorporating reassortant rotavirus strains that protect against human serotypes 1, 2, 4 (and other newer serotypes) may be required. It is hoped that, once safe immunogenic and protective candidate rotavirus vaccines are identified, they can be administered in an acceptable form with no alteration to existing immunization schedules.

89043549. PubMed ID: 3055202. Gram-positive bacteria: an overview and summary of session. Anthony B F; Hill H R. (Department of Pediatrics, Harbor-UCLA Medical Center, Torrance 90509.) Reviews of infectious diseases, (1988 Jul-Aug) 10 Suppl 2 S345-50. Ref: 34. Journal code: 7905878. ISSN: 0162-0886. Pub. country: United States. Language: English.

AB The more pathogenic gram-positive bacteria present a complex array of surface structures to the human or animal host. The cell wall of Staphylococcus aureus has a pattern of surface proteins; the predominant one is protein A. Virulent S. aureus strains may also produce polysaccharide capsules in vivo that impede opsonization and phagocytosis in the absence of anticapsular antibody. Coagulase-negative staphylococci commonly elaborate an exopolysaccharide slime that may promote adherence to plastic surfaces and interfere with host responses. Structure-function relationships for some antiphagocytic M proteins of group A streptococci are now well understood, and recombinant techniques offer the prospect of **multivalent vaccines**. The best known surface protein of group B streptococci is the c (Ibc) protein, which stimulates protective antibody in animals and may be an important virulence factor. Monoclonal antibodies to types Ib, II, and III group B streptococci have also confirmed the presence of multiple immunodeterminants on these antiphagocytic polysaccharides. A protein on the surface of pneumococci has been shown to induce protective antibody and to enhance pneumococcal virulence in mice, suggesting a potential alternative or adjunct to pneumococcal polysaccharide vaccines. Listeria also possess a variety of cell surface structures important in pathogenesis. Surface components are, therefore, critical determinants of the interaction of gram-positive bacteria with the host.

L46 ANSWER 151 OF 162 MEDLINE on STN

88006397. PubMed ID: 3498689. Protection of gnotobiotic rats against dental caries by passive immunization with bovine milk antibodies to Streptococcus mutans. Michalek S M; Gregory R L; Harmon C C; Katz J; Richardson G J; Hilton T; Filler S J; McGhee J R. (Department of Microbiology, University of Alabama at Birmingham 35294.) Infection and immunity, (1987 Oct) 55 (10) 2341-7. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB A **multivalent vaccine** consisting of whole cell antigens of seven strains, representing four serotypes (b, c, d and g), of mutans streptococci was used to hyperimmunize a group of cows. Serum samples from these animals contained immunoglobulin G1 (IgG1) antibody activity to seven serotypes (a to g) of mutans streptococci. Whey obtained from the animal with the highest serum antibody activity, which also contained high levels of IgG1 antibody, was used in passive caries immunity studies. Gnotobiotic rats monoinfected with Streptococcus mutans MT8148 serotype c or Streptococcus sobrinus OMZ176 (d) or 6715 (g) and provided a caries-promoting diet containing immune whey had lower plaque scores, numbers of streptococci in plaque, and degree of caries activity than similarly infected animals given a diet containing control whey obtained from nonimmunized cows. To establish the nature of the protective component(s) present in the immune whey, an ultrafiltrate fraction of the whey was prepared. This preparation contained higher levels of IgG1 anti-S. mutans antibody activity than the immune whey. Rats monoinfected with S. mutans MT8148 and provided with a diet supplemented with 0.1% of this fraction exhibited a degree of caries protection similar to that seen in animals provided a diet containing 100% immune whey. In fact, a diet containing as little as 0.01% of the ultrafiltrate fraction gave some degree of protection against oral S. mutans infection. The active component in the immune whey was the IgG1 anti-S. mutans antibody, since rats monoinfected with S. mutans MT8148 and provided a diet supplemented with purified immune whey IgG1 had significantly reduced plaque scores, numbers of S. mutans in plaque, and caries activity compared with control animals. Prior adsorption of the IgG fraction with killed S. mutans MT8148 whole cells removed antibody activity and abrogated caries protection.

87083387. PubMed ID: 2878919. Morphogenetic expression of Bacteroides nodosus fimbriae in Pseudomonas aeruginosa. Mattick J S; Bills M M; Anderson B J; Dalrymple B; Mott M R; Egerton J R. Journal of bacteriology, (1987 Jan) 169 (1) 33-41. Journal code: 2985120R. ISSN: 0021-9193. Pub. country: United States. Language: English.

AB Type 4 fimbriae are found in a range of pathogenic bacteria, including Bacteroides nodosus, Moraxella bovis, Neisseria gonorrhoeae, and Pseudomonas aeruginosa. The structural subunits of these fimbriae all contain a highly conserved hydrophobic amino-terminal sequence preceding a variable hydrophilic carboxy-terminal region. We show here that recombinant P. aeruginosa cells containing the B. nodosus fimbrial subunit gene under the control of a strong promoter (pL, from bacteriophage lambda) produced large amounts of fimbriae that were structurally and antigenically indistinguishable from those produced by B. nodosus. This was demonstrated by fimbrial isolation and purification, electrophoretic and Western transfer analyses, and immunogold labeling and electron microscopy. These results suggest that type 4 fimbriated bacteria use a common mechanism for fimbrial assembly and that the structural subunits are interchangeable, thereby providing a basis for the development of **multivalent vaccines**.

L46 ANSWER 153 OF 162 MEDLINE on STN

86225981. PubMed ID: 3519829. Opsonic antibodies evoked by hybrid peptide copies of types 5 and 24 streptococcal M proteins synthesized in tandem. Beachey E H; Gras-Masse H; Tarter A; Jolivet M; Audibert F; Chedid L; Seyer J M. Journal of experimental medicine, (1986 Jun 1) 163 (6) 1451-8. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The protective immunogenicity of a hybrid peptide containing tandem copies of types 5 and 24 epitopes was investigated. Carboxy-terminal peptides of the cyanogen bromide-derived fragment 7 (CB7) of type 24 M protein were chemically synthesized, and then extended to include the first 20 residues of the amino-terminus of type 5 M protein. When emulsified in CFA and injected into rabbits without conjugation to a carrier, each of the synthetic hybrid peptides, designated S-M5(1-20)-S-CB7(23-35)C and S-M5(1-20)-S-CB(19-34), evoked opsonic antibodies against both types 5 and 24 streptococci without raising heart tissue-crossreactive immunity. These results suggest that tandem hybrid peptides may provide a new approach to the development of **multivalent vaccines**, not only to different serotypes of group A streptococci but perhaps also to a variety of other infectious agents.

L46 ANSWER 154 OF 162 MEDLINE on STN

85170407. PubMed ID: 6085198. New poliovirus vaccines: a molecular approach. Almond J W; Stanway G; Cann A J; Westrop G D; Evans D M; Ferguson M; Minor P D; Spitz M; Schild G C. Vaccine, (1984 Sep) 2 (3) 177-84. Ref: 38. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This article summarizes recent work on the determinants of antigenicity in poliovirus type 3 and reports on experiments in progress aimed at understanding the molecular basis of attenuation in Sabin's type 3 vaccines. Ways in which this new information might be used to produce alternative, safe, inexpensive, **multivalent vaccines** against polio and other enteroviruses are discussed.

L46 ANSWER 155 OF 162 MEDLINE on STN

85139945. PubMed ID: 2579373. Avian pox: infection and immunity with quail, psittacine, fowl, and pigeon pox viruses. Winterfield R W; Reed W. Poultry science, (1985 Jan) 64 (1) 65-70. Journal code: 0401150. ISSN: 0032-5791. Pub. country: United States. Language: English.

AB Quail, chickens, and turkeys vaccinated with pigeon and fowl pox viruses were not protected against challenge of their immunity with quail pox virus and they developed severe cutaneous lesions of pox. When quail and chickens were vaccinated with quail pox virus and given pigeon and fowl pox challenge viruses, no protection was present. Thus, quail pox virus

had no immunologic relationship to pigeon and fowl pox viruses.
Psittacine pox virus applied as a vaccine in quail and chickens also failed to protect against quail pox virus challenge. However, quail, chickens, and turkeys vaccinated with quail pox virus were protected against quail pox virus challenge. An isolate of psittacine pox virus, applied as a vaccine, protected chickens against challenge with the same virus isolate and also against challenge with two other psittacine pox virus isolates, confirming a close or identical antigenic relationship with each other. When combined in a **multivalent vaccine**, quail, psittacine, and fowl pox viruses induced excellent protection in chickens against challenge with the three respective viruses. The presence or absence of "takes" or reactions following vaccination by the wing web route did not necessarily correlate with the presence or absence of immunity noted from challenge by feather follicle virus application. The role of quail and psittacine pox viruses as potential pathogens for poultry was discussed briefly.

L46 ANSWER 156 OF 162 MEDLINE on STN
85114618. PubMed ID: 6097969. Clinical and serological outcome following the simultaneous inoculation of three bluetongue virus types into sheep. Jeggo M H; Wardley R C; Taylor W P. Research in veterinary science, (1984 Nov) 37 (3) 368-70. Journal code: 0401300. ISSN: 0034-5288. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The simultaneous inoculation of sheep with three different bluetongue virus types resulted in the replication of only two of the virus types and the formation of neutralising antibodies to only those two types and a failure in the production of heterotypic antibodies. This suggests that the present system of control, using **multivalent vaccines** in areas in which a number of bluetongue serotypes exist, should be reappraised.

L46 ANSWER 157 OF 162 MEDLINE on STN
77093218. PubMed ID: 832968. Oral vaccination and **multivalent vaccine** against Pseudomonas aeruginosa keratitis. Gerke J R; Nelson J S. Investigative ophthalmology & visual science, (1977 Jan) 16 (1) 76-80. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.
AB Active immunization against Pseudomonas aeruginosa keratitis and systemic disease in mice was studied. In the first series of experiments, monovalent vaccine, administered orally or intraperitoneally, protected against subsequent corneal and intraperitoneal challenge with the homologous strain of P. aeruginosa; however, oral administration of vaccine elicited less protection than intraperitoneal administration. After both routes, protection was observed at 11 and 32 days post-vaccination, but it was greater at 11 days. In the second series of experiments, **multivalent vaccine** administered intraperitoneally protected against corneal challenge with 56 to 78 percent of 18 strains.

L46 ANSWER 158 OF 162 MEDLINE on STN
76088807. PubMed ID: 812544. Protective properties and haemagglutinins in serum from humans and in serum from mice injected with a new polyvalent Pseudomonas vaccine. Jones R J; Roe E A. British journal of experimental pathology, (1975 Feb) 56 (1) 34-43. Journal code: 0372543. ISSN: 0007-1021. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Mice given single injections of a polyvalent pseudomonas vaccine produced anti-pseudomonas haemagglutinins against the 16 component immunogens of the **multivalent vaccine**. Mice passively immunized with sera from vaccinated mice were protected against lethal challenge by 8/10 strains of Ps. aeruginosa of homologous serotype. Protection by the serum was inversely proportional to the virulence of the challenge strains. Anti-pseudomonas haemagglutinins were always present in sera which passively protected mice against pseudomonas infection. Low levels of anti-pseudomonas haemagglutinins were present in some sera which failed to passively immunize mice against pseudomonas infection. Anti-pseudomonas haemagglutinins and antibodies involved in passive protection were mainly in the IgM fractions of mouse serum. Control human sera contained anti-pseudomonas haemagglutinins against most serotypes of Ps. aeruginosa.

haemagglutinins against some but not all serotypes of Ps. aeruginosa. Sera from both controls and patients with burns passively protected mice against pseudomonas infection.

L46 ANSWER 159 OF 162 MEDLINE on STN
75150202. PubMed ID: 1168603. Vaccination against bovine respiratory disease. Phillip J I. Developments in biological standardization, (1975) 28 501-9. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB Vaccination is but one element in a control programme for bovine respiratory disease. Its laboratory study can be divorced from the others but its field application cannot. The problems associated with the development of effective vaccines fall into two broad groups: multiplicity and ubiquity of pathogens and secondly the identification of the crucial elements in an immune response. Agricultural systems which experience annual outbreaks of respiratory disease attributable to the same pathogen in cattle of specific age have the choice of using passive or active immunity of minimal valency. In the majority of systems the cause and timing of an outbreak cannot be predicted and therefore **multivalent vaccines** are required. Both inactivated and modified live products are available for use against the well-known pathogens. Their relative advantages hinge on the significance attributed to the ability to stimulate the production of particular immunoglobulins at specific body sites and the persistence of the responses. The widely held view that success requires the stimulation of secretory antibodies by intranasal administration of living vaccines is not universally accepted. An assessment of their protective value is not easily made because of the difficulty of reproducing an adequate field challenge in the laboratory. The measurement of serological responses and virus shedding times following challenge are of limited value as alternatives.

L46 ANSWER 160 OF 162 MEDLINE on STN
75150155. PubMed ID: 236208. Problems and progress towards vaccination against bacterial infections of the respiratory tract. Artenstein M S. Developments in biological standardization, (1975) 28 115-25. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB A large number of bacterial species are causative agents of respiratory tract disease. The discussion will center on three infections selected because they represent different problems in control on the basis of epidemiologic and immunochemical factors. Group A hemolytic streptococci are common upper respiratory tract pathogens which may initiate severe non-suppurative sequelae such as rheumatic fever and glomerulonephritis. Recent progress concerning M protein vaccines will be reviewed. Pneumococci are still the most frequent cause of pneumonia at all ages. Pneumococcal vaccines are the prototype for purified polysaccharide vaccines since their effectiveness was demonstrated 30 years ago. The major problem in vaccination is the very large number of capsular serotypes. Pseudomonas aeruginosa represents the relatively new problem of gram-negative bacterial infections in the immunodepressed host. Demonstration of seven immunotypes as the cause of 90% of human infections has led to preparation of a **multivalent vaccine** composed of lipopolysaccharide antigens. Current knowledge of this vaccine will be discussed.

L46 ANSWER 161 OF 162 MEDLINE on STN
72101573. PubMed ID: 4333444. The antigenicity of **multivalent vaccines** for bovine respiratory disease. Schell K; Sanderson R P; Whalen J W; Bittle J L. Cornell veterinarian, (1972 Jan) 62 (1) 101-9. Journal code: 0074245. ISSN: 0010-8901. Pub. country: United States. Language: English.

L46 ANSWER 162 OF 162 MEDLINE on STN
71018626. PubMed ID: 4097599. Active immunoprophylaxis in burns with a new **multivalent vaccine**. Sachs A. Lancet, (1970 Nov 7) 2 (7680) 959-61. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United

Kingdom. Language: English.

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L46 ANSWER 100 OF 162 MEDLINE on STN
96302548. PubMed ID: 8740907. Techniques for genetic engineering in mycobacteria. Alternative host strains, DNA-transfer systems and vectors. Hermans J; de Bont J A. (Department of Food Science, Agricultural University, Wageningen, The Netherlands.) Antonie van Leeuwenhoek, (1996 Apr) 69 (3) 243-56. Ref: 100. Journal code: 0372625. ISSN: 0003-6072. Pub. country: Netherlands. Language: English.

AB The study of mycobacterial genetics has experienced quick technical developments in the past ten years, despite a relatively slow start, caused by difficulties in accessing these recalcitrant species. The study of mycobacterial pathogenesis is important in the development of new ways of treating tuberculosis and leprosy, now that the emergence of antibiotic-resistant strains has reduced the effectiveness of current therapies. The tuberculosis vaccine strain M. bovis BCG might be used as a vector for **multivalent vaccination**. Also, non-pathogenic mycobacterial strains have many possible biotechnological applications. After giving a historical overview of methods and techniques, we will discuss recent developments in the search for alternative host strains and DNA transfer systems. Special attention will be given to the development of vectors and techniques for stabilizing foreign DNA in mycobacteria.

L46 ANSWER 101 OF 162 MEDLINE on STN
96274272. PubMed ID: 8684875. Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional pharmacovigilance centres and pasteur-merieux serums et vaccins. Jonville-Bera A P; Autret E; Galy-Eyraud C; Hessel L. (Department of Clinical Pharmacology, Hopital Bretonneau, Tours, France.) Pediatric infectious disease journal, (1996 Jan) 15 (1) 44-8. Journal code: 8701858. ISSN: 0891-3668. Pub. country: United States. Language: English.

AB BACKGROUND: Thrombocytopenic purpura (TP) after vaccination with measles, mumps and rubella has occasionally been reported. OBJECTIVES: To evaluate the incidence and characteristics of thrombocytopenic purpura reported in France after measles, mumps or rubella vaccination with monovalent or **multivalent vaccines**. METHODS: A retrospective epidemiologic survey was conducted. All confirmed cases of TP reported spontaneously either to the French Regional Pharmacovigilance Centres or to the manufacturer (Pasteur-Merieux Serums et Vaccins) between 1984 and June 30, 1992, were reviewed. RESULTS: Sixty cases of TP in children between 1 and 11 years of age occurred 2 to 45 days after administration of 1 of 7 vaccines. The reported incidence of TP varied from 0.17 and 0.23/100,000 doses of measles or rubella vaccines, respectively, given alone to 0.87/100,000 doses of combined measles-rubella vaccines and 0.95/100,000 doses of the measles-mumps-rubella vaccine. The mean platelet count was 8000 +/- 6000/mm3 and was lower than 10,000/mm3 in 58% of cases. The immediate outcome was favorable in 89.5% of cases. CONCLUSIONS: According to the clinical course and biologic findings, vaccine-associated TP appears to be similar to that occurring after natural measles or rubella infections and is not distinguishable from acute childhood idiopathic thrombocytopenic purpura not associated with vaccination. Such observations, combined with a clear temporal relationship between measles-mumps-rubella vaccination and the occurrence of TP, make a causal relationship highly plausible. Nevertheless the incidence of these events remains relatively low with a favorable immediate outcome.

L46 ANSWER 102 OF 162 MEDLINE on STN
96215657. PubMed ID: 8645110. Immunisation with DNA polynucleotides protects mice against lethal challenge with St. Louis encephalitis virus. Phillpotts R J; Venugopal K; Brooks T. (Microbiology Group, Chemical and Biological Defence Establishment, Porton Down, Wiltshire, U.K.) Archives of virology, (1996) 141 (3-4) 743-9. Journal code: 7506870. ISSN: 0304-8608. Pub. country: Austria. Language: English.

AB In vivo transfection by intramuscular injection with plasmids expressing the immunogenic proteins of microbial pathogens has considerable potential as a vaccination strategy against many pathogens of both man and animals. Here we report that weanling mice given a single intramuscular injection of 50 micrograms of a plasmid, pSLE1 expressing the St. Louis encephalitis virus (SLE) prM/E protein under the control of the cytomegalovirus immediate early protein promoter produced SLE-specific antibody and were protected against lethal challenge with the virulent virus. Polynucleotide vaccine technology provides a unique opportunity to produce vaccines against flavivirus diseases of low incidence cheaply and rapidly, and to produce **multivalent vaccines** such as would be required for immunisation against dengue virus disease.

L46 ANSWER 103 OF 162 MEDLINE on STN
96162088. PubMed ID: 8568291. Protection against papillomavirus with a polynucleotide vaccine. Donnelly J J; Martinez D; Jansen K U; Ellis R W; Montgomery D L; Liu M A. (Department of Virus and Cell Biology, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.) Journal of infectious diseases, (1996 Feb) 173 (2) 314-20. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Genital infections with human papillomavirus (HPV) are increasingly recognized as a significant source of human disease; HPV is now implicated in up to 90% of cervical carcinomas. Neutralizing antibodies against papillomaviruses recognize conformational epitopes formed when viral capsid proteins assemble into virions or virus-like particles. Immunization with plasmid DNA encoding the major viral capsid protein L1 was studied as a means of inducing neutralizing antibodies and protection against virus challenge. In a cottontail rabbit papillomavirus (CRPV) model, immunization with plasmid DNA encoding L1 elicited conformationally specific neutralizing antibodies and provided immunity against papilloma formation upon challenge with CRPV. Immunization with DNA encoding the capsid protein may provide a means of protecting humans against HPV and would simplify the production of **multivalent vaccines** by combining plasmids that encode the viral capsid proteins of different strains. This may be of importance given the multiplicity of HPV types capable of causing disease.

L46 ANSWER 104 OF 162 MEDLINE on STN
96146050. PubMed ID: 8581171. Monoclonal antibody recognition of members of the meningococcal P1.10 variable region family: implications for serological typing and vaccine design. Suker J; Feavers I M; Maiden M C. (Division of Bacteriology, National Institute for Biological Standards and Control, Potters Bar, Herts, UK.) Microbiology (Reading, England), (1996 Jan) 142 (Pt 1) 63-9. Journal code: 9430468. ISSN: 1350-0872. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Identification of antigenic variants of the PorA protein of Neisseria meningitidis with specific mAbs (serosubtyping) is used in meningococcal strain characterization and the resultant data has been exploited in the design of novel **multivalent vaccines** against this important pathogen. The reactivity of the P1.10 serosubtyping mAb MN20F4.17 with eight members of the meningococcal P1.10 variable region (VR) family (prototype P1.10 and variants P1.10a-P1.10g), identified by nucleotide sequence analysis of porA genes, was investigated. Analysis of overlapping synthetic octapeptides by ELISA demonstrated that the peptide sequence, QNQRPTL, present only in the prototype P1.10, was sufficient for binding of the mAb. A linear peptide of 14 amino acids, containing the minimum epitope, inhibited binding of mAb MN20F4.17 to whole cells in a competitive ELISA. This binding was weak compared with a tethered peptide or the native protein. In whole-cell ELISA or dot-blot assays using low concentrations of mAb MN20F4.17 only the prototype P1.10 was detected. However, when higher concentrations of antibody were used the prototype P1.10 was detected, together with variants P1.10a, P1.10c and P1.10e by whole-cell ELISA and P1.10a and P1.10c by the immunoblot technique. The variants P1.10b, P1.10d, P1.10f and P1.10g showed no reactivity with mAb under any of the conditions tested. A survey of the porA genes in serogroup B and C strains revealed that the P1.10a variant, rather than the prototype P1.10,

has the most common member of the P1.16 ... family in England and Wales.
These data illustrate: (i) the problems associated with epidemiological analyses that rely solely on monoclonal antibodies; (ii) the importance of using defined assay conditions for serosubtyping; and (iii) that genetical analyses provide more reliable information than serological data based on murine reagents for the design of candidate vaccines that include PorA.

L46 ANSWER 105 OF 162 MEDLINE on STN
96126014. PubMed ID: 8589153. Prospects for a vaccine to prevent Lyme disease in humans. Wormser G P. (Division of Infectious Diseases, Westchester County Medical Center, Valhalla, New York 10595, USA.) Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, (1995 Nov) 21 (5) 1267-74. Ref: 113. Journal code: 9203213. ISSN: 1058-4838. Pub. country: United States. Language: English.

AB Vaccination with recombinant outer-surface protein A (OspA) preparations has been highly successful in protecting laboratory animals against challenge by strains of Borrelia burgdorferi closely related to the one from which the OspA was derived. Humoral immunity is sufficient for protection. Against natural infection introduced by ticks, the vaccine-induced immune response may begin to take effect in the tick itself--i.e., before the spirochete enters the host--and may extend to a broader spectrum of strains of B. burgdorferi than are represented in the vaccine. Single recombinant OspA vaccine preparations are currently being evaluated in two large-scale efficacy trials in adults in the United States. Greater heterogeneity among B. burgdorferi strains in Europe than among those in the United States will likely necessitate the development of a vaccine containing antigens from multiple strains; a **multivalent vaccine** may or may not be needed in the United States.

L46 ANSWER 106 OF 162 MEDLINE on STN
96037961. PubMed ID: 7571364. The protective efficacy of cloned Moraxella bovis pili in monovalent and **multivalent vaccine** formulations against experimentally induced infectious bovine keratoconjunctivitis (IBK). Lepper A W; Atwell J L; Lehrbach P R; Schwartzkoff C L; Egerton J R; Tennent J M. (CSIRO Division of Animal Health, Animal Health Research Laboratory, Parkville, Vic., Australia.) Veterinary microbiology, (1995 Jul) 45 (2-3) 129-38. Journal code: 7705469. ISSN: 0378-1135. Pub. country: Netherlands. Language: English.

AB Calves were vaccinated with cloned Moraxella bovis pili of serogroup C (experiment 1) or B (experiment 2) either as a monovalent formulation or as part of a multivalent preparation with pili of six other serogroups. Within 4 weeks of the second vaccine dose vaccinated calves and non-vaccinated controls were challenged via the ocular route with either virulent M. bovis strain Dal2d (serogroup C) or M. bovis strain 3WO7 (serogroup B) in experiments 1 and 2, respectively. Calves vaccinated with **multivalent vaccines** had significantly lower antibody titres than those vaccinated with monovalent preparations. Nevertheless, the levels of protection against infectious bovine keratoconjunctivitis (IBK) achieved with **multivalent vaccines** were 72% and 83% for the groups challenged with M. bovis strains of serogroups B and C, respectively. The serogroup C monovalent vaccine gave 100% protection against experimentally induced IBK and M. bovis isolates cultured from the eyes 6 days post-challenge were identified as belonging solely to serogroup C. Unexpectedly, only 25% protection was achieved against homologous strain challenge of calves that received the monovalent serogroup B vaccine. Furthermore, the majority of M. bovis isolates recovered from calves in this group belonged to serogroup C, as did half of those isolates cultured from the **multivalent vaccinates**. The remaining bacterial isolates from the latter group, together with all isolates from the non-vaccinated controls, belonged to serogroup B. Results are consistent with the hypothesis that derivatives of the serogroup B challenge inoculum had expressed serogroup C pilus antigen within 6 days of the challenge, possibly as a result of pilus gene inversion occurring in response to the presence of specific antibody in eye tissues and tears.

L46 ANSWER 107 OF 162 MEDLINE on STN
95394851. PubMed ID: 7545156. Expression of Shigella dysenteriae serotype 1 O-antigenic polysaccharide by Shigella flexneri aroD vaccine candidates and different S. flexneri serotypes. Falt I C; Schweda E K; Klee S; Singh M; Floderus E; Timmis K N; Lindberg A A. (Department of Immunology, Microbiology, Pathology, and Infectious Diseases, Karolinska Institute, Huddinge, Sweden.) Journal of bacteriology, (1995 Sep) 177 (18) 5310-5. Journal code: 2985120R. ISSN: 0021-9193. Pub. country: United States. Language: English.

AB The potential utility of Shigella flexneri aroD vaccine candidates for the development of bi- or **multivalent vaccines** has been explored by the introduction of the genetic determinants rfp and rfb for heterologous O antigen polysaccharide from Shigella dysenteriae serotype 1. The serotype Y vaccine strain SFL124 expressed the heterologous antigen qualitatively and quantitatively well, qualitatively in the sense of the O antigen polysaccharide being correctly linked to the S. flexneri lipopolysaccharide R3 core oligosaccharide and quantitatively in the sense that typical yields were obtained, with ratios of homologous to heterologous O antigen being 4:1 for one construct and 1:1 for another. Moreover, both polysaccharide chains were shown to be linked to position O-4 of the subterminal D-glucose residue of the R3 core. In contrast to the hybrid serotype Y SFL124 derivatives, analogous derivatives of serotype 2a vaccine strain SFL1070 did not elaborate a complete heterologous O antigen. Such derivatives, and analogous derivatives of rough, O antigen-negative mutants of SFL1070, formed instead a hybrid lipopolysaccharide molecule consisting of the S. flexneri lipid A R3 core with a single repeat unit of the S. dysenteriae type 1 O antigen. Introduction of the determinants for the S. dysenteriae type 1 O antigen into a second serotype 2a strain and into strains representing other serotypes of S. flexneri, revealed the following for the expression of the heterologous O antigen: serotypes 1a, 1b, 2a, and 5a did not produce the heterologous O antigen, whereas serotypes 2b, 3a, 3b, 4a, 4b, 5b, and X did.

L46 ANSWER 108 OF 162 MEDLINE on STN
95366223. PubMed ID: 7639013. Synthesis and characterization of a polyvalent Escherichia coli O-polysaccharide-toxin A conjugate vaccine. Cryz S J Jr; Que J O; Cross A S; Furer E. (Swiss Serum and Vaccine Institute, Berne.) Vaccine, (1995 Apr) 13 (5) 449-53. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A 12-valent Escherichia coli O-polysaccharide (O-PS)-toxin A conjugate vaccine was formulated. Nonpyrogenic, low-molecular-weight O-PS was derived from lipopolysaccharides (LPS) of the following serotypes: O1,O2,O4,O6,O7,O8,O12, O15,O16,O18,O25, and O75. Individual O-PS were covalently coupled to Pseudomonas aeruginosa toxin A using adipic acid dihydrazide as a spacer molecule and carbodiimide as a coupling agent. On a weight basis, the final **multivalent vaccine** was composed of 43% O-PS and 57% toxin A. The vaccine was nontoxic nad nonpyrogenic in anti-LPS immunoglobulin G (IgG) antibody titers. When passively transferred to mice, immune rabbit IgG conferred statistically significant ($p < 0.05$) protection against a challenge with 9 of the 12 vaccine serotypes. For two serotypes, although the mortality rate declined by > or 50% in the passively immunized versus the control group, the difference did not reach statistical significance. The degree of protection provided by passively transferred IgG was influenced by both the anti-LPS antibody levels in the IgG preparation and the virulence of the challenge strain. Active immunization of mice with either conjugate vaccine or killed E. coli whole cells did not confer protection. This was most probably due to the fact that these antigens induced a meagre anti-LPS IgG antibody response.

L46 ANSWER 109 OF 162 MEDLINE on STN
95351605. PubMed ID: 7625656. Manufacturing issues for **multivalent vaccines**. Elliott A Y. (Merck & Co., Inc., Merck Manufacturing Division, West Point, Pennsylvania 19486-0004, USA.) Annals of the New York Academy of Sciences, (1995 May 31) 754 23-6. Journal code: 7506858. ISSN:

L46 ANSWER 110 OF 162 MEDLINE on STN
95303546. PubMed ID: 7784125. The development of oral vaccines against parasitic diseases utilizing live attenuated Salmonella. Chatfield S N; Roberts M; Dougan G; Hormaeche C; Khan C M. (Medeva Vaccine Research Unit, Imperial College of Science Technology and Medicine, London, UK.) Parasitology, (1995) 110 Suppl S17-24. Ref: 56. Journal code: 0401121. ISSN: 0031-1820. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Genetically defined, live attenuated Salmonella vaccines are proving useful both as oral vaccines against salmonellosis and for the development of **multivalent vaccines** based on the expression of heterologous antigens in such strains. Several candidate attenuated S. typhi strains are at present being evaluated as new single dose oral typhoid vaccines in human volunteers. The emergence of such a vaccine will facilitate the development of **multivalent vaccines** for humans. Many antigens from different infectious organisms have been expressed in attenuated Salmonella. A focus of this work has been on developing vaccines against parasitic diseases. This review will summarize the efforts that have been made in this area.

L46 ANSWER 111 OF 162 MEDLINE on STN
95255649. PubMed ID: 7537703. The Salmonella ompC gene: structure and use as a carrier for heterologous sequences. Puente J L; Juarez D; Bobadilla M; Arias C F; Calva E. (Departamento de Microbiologia Molecular, Universidad Nacional Autonoma de Mexico, Cuernavaca.) Gene, (1995 Apr 14) 156 (1) 1-9. Journal code: 7706761. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB The Salmonella typhi (St) ompC gene codes for a major outer membrane protein (OMP) that is highly expressed in both low and high osmolarity. By hybridization studies with the entire gene or with segments thereof, ompC was found to be highly conserved within 11 different Salmonella serotypes, with the exception of S. arizonae. The study included several St isolates from Mexico and Indonesia. Variation was only detected in two (e and f) of the seven regions previously found to vary between St and E. coli ompC. Chimeric OmpC proteins, carrying a rotavirus VP4 capsid protein epitope, are well recognized by a specific monoclonal antibody (mAb) against this epitope, either in OMP preparations (by enzyme-linked immunosorbent assay; ELISA) or intact cells (by ELISA and immunogold-labelling), indicating that regions c and f are oriented towards the cell surface and are probably exposed. As has been shown before for other regulated OMP, this experimental approach could be useful for the presentation of heterologous epitopes in order to gain knowledge about porin topology, for testing the effect of altered porin surface epitopes on bacterial physiology, or else, in the development of **multivalent vaccines**.

L46 ANSWER 112 OF 162 MEDLINE on STN
95161918. PubMed ID: 7858406. Perspectives and limitations of the mycobacterial expression system. Villar C; Benitez J. (Centro Nacional de Investigaciones Cientificas, Havana, Cuba.) Archives of medical research, (1994 Winter) 25 (4) 451-3. Journal code: 9312706. ISSN: 0188-4409. Pub. country: Mexico. Language: English.

AB To develop **multivalent vaccines** expressing foreign antigens in BCG strains, a genetic system for BCG and Mycobacterium smegmatis is being developed that uses vectors derived from the M. fortuitum pAL5000 plasmid. In this paper we present recent advances of our laboratory in this line of research: i) optimal conditions for M. fortuitum electroporation, ii) demonstration that host range properties of pAL5000-based vectors depend on certain open reading frames, iii) cloning of expression signals derived from the BCG Moreaux 65 kD antigen, and iv) construction of expression vectors for M. smegmatis.

L46 ANSWER 113 OF 162 MEDLINE on STN
95148502. PubMed ID: 7845943. Prevention of periodontal diseases in adults: strategies for the future. Jeffcoat M K. (Department of

) Preventive medicine, (1994 Sep) 23 (5) 704-8. Journal code: 0322116. ISSN: 0091-7435. Pub. country: United States. Language: English.

AB Gingivitis and periodontitis are the most prevalent periodontal diseases in adults. Gingivitis is characterized by inflammation of the gingiva without loss of connective tissue attachment to the teeth while periodontitis results in loss of attachment and alveolar bone and may lead to tooth loss. Gingivitis is highly prevalent in adults in the United States, and up to 70% of adults have at least mild periodontitis. In only a small proportion of adults (< 15%) does periodontitis progress to severe disease. The etiology of periodontal disease is infection with pathogenic dental plaque bacteria in a susceptible host. Strategies for preventing periodontal diseases therefore may intervene at the level of the initiation of the inflammatory process, or by preventing the progression of bone and attachment loss in periodontitis. Improved mechanical and chemical plaque control as well as improved restorative materials to facilitate plaque removal continue to enhance the patient's ability to control the plaque bacteria. Strategies to target prevention to the patients who need it most include risk factor assessment, new diagnostic methods, and further elucidation of the natural history of periodontal disease. Further study of the etiology and pathophysiology of periodontitis will aid in the prevention of further destruction through targeted use of local and systemic antibiotics and well as drugs to aid in the host response. Ultimately research may yield **multivalent vaccines** to be used in high-risk patients.

L46 ANSWER 114 OF 162 MEDLINE on STN

95056183. PubMed ID: 7966729. Phase I clinical trial of vaginal mucosal immunization for recurrent urinary tract infection. Uehling D T; Hopkins W J; Dahmer L A; Balish E. (Department of Surgery (Urology), University of Wisconsin Medical School, Madison.) Journal of urology, (1994 Dec) 152 (6 Pt 2) 2308-11. Journal code: 0376374. ISSN: 0022-5347. Pub. country: United States. Language: English.

AB In a phase I clinical trial to test safety and patient acceptance 25 women with a history of recurrent urinary tract infections but no identifiable anatomic abnormality received a **multivalent vaccine** instilled into the vagina. The vaccine contained 6 heat-killed Escherichia coli strains and 4 nonE. coli uropathogens. Only minimal adverse reactions were observed in the 5-month period following immunization. Total vaginal and urinary IgG and IgA increased significantly ($p < 0.01$ by repeated measures analysis of variance). Serum antibodies to some of the nonE. coli strains but not to the E. coli strains increased after vaginal immunization. While efficacy is yet to be shown, this study indicates that this vaginally applied urinary tract infection vaccine is well tolerated, and capable of increasing vaginal and urinary antibody.

L46 ANSWER 115 OF 162 MEDLINE on STN

95007437. PubMed ID: 7923051. Malaria vaccine development. Jones T R; Hoffman S L. (Malaria Program, Naval Medical Research Institute, Bethesda, Maryland.) Clinical microbiology reviews, (1994 Jul) 7 (3) 303-10. Ref: 105. Journal code: 8807282. ISSN: 0893-8512. Pub. country: United States. Language: English.

AB The malaria parasite life cycle presents several targets for attack, but these different parts of the life cycle are susceptible to different types of host immune response. For example, the sporozoite is most sensitive to immune antibody, while liver stage parasites can be eliminated by cytotoxic T lymphocytes. Attachment of merozoites to erythrocytes, on the other hand, can be blocked by antibody. Convincing experimental evidence shows that completely protective immunity to malaria can be induced. The challenge now is to design recombinant or synthetic vaccines that induce the right types of immune responses to specific life cycle stages. This requires the identification and characterization of B- and T-lymphocyte epitopes expressed by the parasite or by parasitized host cells. These epitopes must be incorporated into a delivery system that maximizes the interaction between the vaccine epitopes and the host immune system. Many epitopes from several parts of the life cycle are already characterized;

development of **multivalent vaccines**, that is, vaccines which contain immunogens from more than one part of the life cycle, is a promising area for research efforts.

L46 ANSWER 116 OF 162 MEDLINE on STN
94363858. PubMed ID: 8082259. Purification of 31/32 kDa proteins of adult Schistosoma japonicum and studies on their protective immunity. Shen D W; Li Y L; Hang J J; Shi Y E. (Department of Parasitology, Xianning Medical College.) Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases, (1993) 11 (4) 241-3. Journal code: 8709992. ISSN: 1000-7423. Pub. country: China. Language: Chinese.

AB Schistosoma japonicum adult worm 31/32 kDa proteins (Sj 31/32) were separated on polyacrylamide slab gels and purified by electrophoretic elution. These purified proteins were used to immunize mice in order to observe their protective immunity against challenge. The results of SDS-PAGE,EITB and ELISA indicated that the 31/32 kDa proteins separated and purified by means of these methods were pure and active. It was assumed that Sj 31/32 proteins could reduce worm burden and inhibit the fecundity of schistosome and formation of egg granuloma. The results suggested that 31/32 kDa S. japonicum proteins might be an important component of a **multivalent vaccine** against schistosomiasis japonica (Figs. 1-4).

L46 ANSWER 117 OF 162 MEDLINE on STN
94295253. PubMed ID: 7912871. Antigenic competition in a multivalent foot rot vaccine. Hunt J D; Jackson D C; Brown L E; Wood P R; Stewart D J. (Department of Microbiology, University of Melbourne, Parkville, Victoria, Australia.) Vaccine, (1994 Apr) 12 (5) 457-64. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The antigenic competition that occurs when pilus antigens of different serogroups are combined in **multivalent vaccines** for foot rot has been investigated using recombinant pilus antigens. Our prototype vaccine contains pili from nine serogroups of Dichelobacter nodosus which are expressed in Pseudomonas aeruginosa. Sheep inoculated with this **multivalent vaccine** were not as well protected against foot rot as those given the monovalent vaccine. Levels of agglutinating and total antibody specific for any particular pili serogroup were found to be significantly reduced in sheep vaccinated with six or more closely related pili. This effect was more pronounced for agglutinating antibody, which is thought to mediate protection, but was also observed with total antibody levels measured by ELISA. The antigenic competition was not associated with the total antigen load as a tenfold higher dose of monovalent pili induced high titres of antibody. Furthermore, distributing the vaccine to four sites, each draining to a different lymph node, failed to overcome the competition. Experiments with mixtures of monospecific sera indicate that the phenomenon is unlikely to be due to blocking of serogroup-specific protective antibodies by an excess of cross-reactive non-protective antibody elicited by heterologous pili.

L46 ANSWER 118 OF 162 MEDLINE on STN
94233851. PubMed ID: 8178558. Purification of antibody-antigen complexes containing recombinant SIV proteins: comparison of antigen and antibody-antigen complexes for immune priming. Randall R E; Young D; Hanke T; Szawlowski P; Botting C. Vaccine, (1994 Mar) 12 (4) 351-8. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This paper describes a general procedure for the two-step purification of recombinant proteins as antibody-antigen complexes in which there is no uncomplexed antibody or antigen. In this way, immune complexes containing the p17, p27, vpr and vpx proteins of simian immunodeficiency virus (SIV) have been purified. Antibody-antigen complexes are more immunogenic than antigen when administered either alone or with alum. The significance of the work is that this general method could be modified for the manufacture of immune complexes for incorporation into **multivalent vaccines**.

94212559. PubMed ID: 7909183. Protective antibody titres and antigenic competition in multivalent Dichelobacter nodosus fimbrial vaccines using characterised rDNA antigens. Raadsma H W; O'Meara T J; Egerton J R; Lehrbach P R; Schwartzkoff C L. (Department of Animal Health, University of Sydney, Camden, N.S.W., Australia.) Veterinary immunology and immunopathology, (1994 Mar) 40 (3) 253-74. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.

AB The relationship between K-agglutination antibody titres and protection against experimental challenge with Dichelobacter nodosus, the effect of increasing the number of D. nodosus fimbrial antigens, and the importance of the nature of additional antigens in **multivalent vaccines** on antibody response and protection against experimental challenge with D. nodosus were examined in Merino sheep. A total of 204 Merino sheep were allocated to one of 12 groups, and vaccinated with preparations containing a variable number of rDNA D. nodosus fimbrial antigens. The most complex vaccine contained ten fimbrial antigens from all major D. nodosus serogroups, while the least complex contained a single fimbrial antigen. In addition to D. nodosus fimbrial antigens, other bacterial rDNA fimbrial antigens (Moraxella bovis Da12d and Escherichia coli K99), and bovine serum albumin (BSA) were used in some vaccines. Antibody titres to fimbrial antigens and BSA were measured by agglutination and ELISA tests, respectively. Antibody titres were determined on five occasions (Weeks 0, 3, 6, 8, and 11 after primary vaccination). All sheep were exposed to an experimental challenge with virulent isolates of D. nodosus from either serogroup A or B, 8 weeks after primary vaccination. For D. nodosus K-agglutinating antibody titres, a strong negative correlation between antibody titre and footrot lesion score was observed. This relationship was influenced by the virulence of the challenge strain. Increasing the number of fimbrial antigens in experimental rDNA D. nodosus fimbrial vaccines resulted in a linear decrease in K-agglutinating antibody titres to individual D. nodosus serogroups. Similarly, a linear decrease in protection to challenge with homologous serogroups was observed as the number of D. nodosus fimbrial antigens represented in the vaccine increased. The reduction in antibody titres in multicomponent vaccines is thought to be due to antigenic competition. The level of competition between individual antigens is not constant and appears to be related to the immunodominance (nature) of the competing antigens. Both BSA ELISA, and M. bovis K-agglutinating antibody titres were adversely affected by the presence of two D. nodosus fimbrial preparations, whereas the antigenicity of E. coli K99 was unchanged by the presence of two additional D. nodosus antigens. Further studies are required to determine the step(s) in the immune response which are influenced by antigenic competition. Our results suggest that antigen presentation, particularly following primary vaccination, is the step most strongly influenced by antigenic competition.

L46 ANSWER 120 OF 162 MEDLINE on STN
94209042. PubMed ID: 8157445. Live attenuated vaccine vectors. Mekalanos J J. (Harvard Medical School.) International journal of technology assessment in health care, (1994 Winter) 10 (1) 131-42. Ref: 65. Journal code: 8508113. ISSN: 0266-4623. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Several different live attenuated vaccine vectors currently are under development. These vaccines are composed of living viruses or bacteria that are innocuous to the host but can replicate in host tissues and induce immune responses. The genes encoding foreign antigens can be inserted into these vectors to produce **multivalent vaccines** that promise to induce immunity to more than one target disease after the administration of a single dose of vaccine.

L46 ANSWER 121 OF 162 MEDLINE on STN
94154521. PubMed ID: 8111241. Oral immunization: turning fantasy into reality. Manganaro M; Ogra P L; Ernst P B. (Department of Pediatrics, University of Texas Medical Branch, Galveston 77573-0366.) International archives of allergy and immunology, (1994) 103 (3) 223-33. Ref: 82.

Journal code: 9211082. ISSN: 1018-2438. Pub. country: Switzerland.
Language: English.

AB The application of oral immunization as the primary means to deliver **multivalent vaccines** to large populations has many theoretical advantages. However, widespread success in achieving protective immunity against these diseases through oral immunization requires additional understanding of the basic mechanisms of host resistance in the mucosal tissues. Fundamental issues, such as the lineage and repertoire or regulatory pathway of mucosal effector cells, are only now just beginning to be understood. A more comprehensive understanding of these issues could greatly enhance our success at designing and applying successful oral immunization programs.

L46 ANSWER 122 OF 162 MEDLINE on STN
94095227. PubMed ID: 7505770. Recombinant vaccines against ovine footrot. O'Meara T J; Egerton J R; Raadsma H W. (Department of Animal Health, University of Sydney, Camden, New South Wales, Australia.) Immunology and cell biology, (1993 Oct) 71 (Pt 5) 473-88. Ref: 87. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB For the past 20 years footrot vaccines have evolved from simple bacterins to highly specific recombinant DNA (rDNA) fimbrial vaccines. The development of these vaccines has left a trail of discoveries, challenges and solutions; these processes continue as we move closer to understanding the requirements of a footrot vaccine. The initial whole cell vaccines were unsuccessful due to the short duration of immunity and incorporation of limited serotypes. A multistrain vaccine eliminated the problem of serotype inclusion, although the duration of immunity in many cases is still inadequate. The proteases of Dichelobacter nodosus appear to be cross protective; however, little is known of their ability to protect sheep against footrot. The major protective immunogen is the bacterial fimbriae, which also forms the basis for the K-agglutination serotyping system. K-agglutinin titre correlates directly with resistance to challenge. The protective fimbrial epitope is conformationally dependent, suggesting little advantage in the development of synthetic peptide vaccines. To enhance the efficiency of vaccine production D. nodosus fimbrial genes were eventually cloned and successfully expressed in Ps. aeruginosa. Monovalent vaccines based on recombinant fimbriae are omnipotent, inducing high levels of agglutinins and long lasting immunity. In **multivalent vaccines**, on the other hand, incorporation of each additional serogroup into the vaccine results in reduced efficacy both in terms of reduced K-agglutinin titres and reduced protection following challenge. The least effective are multivalent formulations representing all major serogroups. In addition, considerable genetic variation has been observed in the ability of sheep to respond optimally to each serogroup in a **multivalent vaccine**. Results show that the limitation of the sheep to mount an effective immune response, rather than the quality or quantity of the immunogen, limits the efficacy of current footrot vaccines. Studies are being undertaken to examine in detail the immune response of sheep to potentially highly effective footrot vaccines.

L46 ANSWER 123 OF 162 MEDLINE on STN
94095219. PubMed ID: 8270268. Recombinant fowlpox virus vaccines for poultry. Boyle D B; Heine H G. (CSIRO Division of Animal Health, Australian Animal Health Laboratory, Geelong, Victoria.) Immunology and cell biology, (1993 Oct) 71 (Pt 5) 391-7. Ref: 40. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB The intensive poultry industries rely heavily upon the use of vaccines for disease control. Viral vector based vaccines offer new avenues for the development of vaccines for effective disease control in poultry. Techniques developed for the construction of recombinant vaccinia viruses have been readily adapted to the construction of recombinant viruses based on fowlpox virus (rFPV). The ability to insert several genes into the large genome of fowlpox may enable the development of **multivalent vaccines** and vaccines incorporating immune response modifiers such as lymphokines. Newcastle disease, avian influenza, infectious bursal disease and Marek's disease antigens expressed by rFPV have been shown to

substantial improvement in vaccine efficacy. Recombinant FPV will be a valuable adjunct to conventional vaccines currently in widespread use. Whether rFPV or other vector based vaccines can circumvent the problems of vaccination in the presence of high maternally derived antibodies is yet to be resolved. The observation that avipoxvirus recombinants may be suitable for the vaccination of non-avian species provides an added dimension to vaccines based on FPV or other avipoxviruses. Recombinant FPV will find a useful role in poultry disease control when used in conjunction with conventional vaccines.

L46 ANSWER 124 OF 162 MEDLINE on STN
94023450. PubMed ID: 7692575. Recombinant hepatitis B surface antigen as a carrier of human immunodeficiency virus epitopes. Michel M L; Mancini M; Schlienger K; Tiollais P. (Unite de Recombinaison et Expression genetique, INSERM-U.163, Institut Pasteur, Paris.) Research in virology, (1993 Jul-Aug) 144 (4) 263-7. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Eukaryotic cells transformed with a plasmid expression vector are able to synthesize and assemble HBsAg, a complex multimeric lipoprotein particle. Hybrid particles carrying HIV1 antigenic determinants were constructed and injected into monkeys. A complete immune response including neutralizing antibodies, proliferative and cytotoxic T-cell activities was obtained. Thus, such HIV/HBsAg hybrid particles could be a new approach to **multivalent vaccination**.

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L46 ANSWER 75 OF 162 MEDLINE on STN
1999053609. PubMed ID: 9839874. Homologous protection but lack of heterologous-protection by various species and types of Bartonella in specific pathogen-free cats. Yamamoto K; Chomel B B; Kasten R W; Chang C C; Tseggai T; Decker P R; Mackowiak M; Floyd-Hawkins K A; Pedersen N C. (Department of Population Health and Reproduction, School of Veterinary Medicine, University of California, Davis 95616, USA.) Veterinary immunology and immunopathology, (1998 Oct 23) 65 (2-4) 191-204. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.

AB Cat-scratch disease (CSD) is caused by Bartonella henselae, and possibly by B. clarridgeiae. In immuno-compromised persons, B. henselae is one of the agents causing bacillary angiomatosis. Domestic cats are the main reservoir of these bacteria, which are transmitted primarily from cat to cat by fleas. Possible strategies to prevent the spread of infection among cats are to eliminate flea infestation or to prophylactically immunize cats. In order to develop an appropriate vaccine, it is important to determine if cats become resistant to re-infection by the same strain or various types or species of Bartonella. In a series of experiments, 21 SPF cats were experimentally infected by the intradermal route with 10(5)-10(10) colony-forming units/ml of either B. henselae type II (17 cats), or a new strain 'Humboldt' isolated from a mountain lion (4 cats). The cats were bled weekly to every other week for determination of bacteremia and specific antibody production. After they cleared their infection, they were challenged by a homologous or heterologous strain of Bartonella: 10 cats were challenged with B. henselae type II, three cats with B. henselae type I, four cats with B. clarridgeiae and four cats with the 'Humboldt' strain. Seven of these cats received a third inoculum dose resulting in three cats sequentially infected with sequence B. henselae type II/B. henselae type II/'Humboldt', two cats with sequence B. henselae type II/'Humboldt'/B. clarridgeiae, and two cats with the sequence 'Humboldt'/B. henselae type II/'Humboldt'. All cats challenged with a homologous strain remained abacteremic after challenge and had an increased IgG antibody titer. All cats challenged with either a different Bartonella species or type became bacteremic. The few cats receiving a third inoculum with a strain homologous to the initial strain remained abacteremicafter that challenge. All cats infected with B. clarridgeiae

infected cats and 22% of the 'Humboldt'-infected cats (p=0.008). The duration of bacteremia was significantly longer in B. henselae primary-infected cats (mean: 34 weeks) than B. henselae heterologously challenged cats (mean: 9 weeks) (p=0.014). These data clearly indicate the lack of cross-protection between B. henselae and B. clarridgeiae and furthermore, indicate the lack of protection between B. henselae types I and II, and a wildlife isolate. A vaccine strategy for CSD prevention in domestic cats will require a **multivalent vaccine** approach.

L46 ANSWER 76 OF 162 MEDLINE on STN
1998444397. PubMed ID: 9767430. Human and murine T-cell responses to allelic forms of a malaria circumsporozoite protein epitope support a polyvalent vaccine strategy. Zevering Y; Khamboonruang C; Good M F. (Queensland Institute of Medical Research, Brisbane, Australia.) Immunology, (1998 Jul) 94 (3) 445-54. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mouse models and a recent vaccine trial have indicated the importance of T-cell immunity to the circumsporozoite protein (CSP) of malaria sporozoites. One of the major impediments for the development of a CSP-based vaccine is that human T-cell epitopes, identified on the CSP, span regions of significant point mutational polymorphism. Studies with human and mouse T-cell clones have indicated that this polymorphism affects T-cell cross-reactivity to Th2R and Th3R, the two most polymorphic and immunodominant epitopes. We extend this observation with polyclonal human T-cell lines, from 11 donors, raised to known variants of Th2R. These lines showed limited but variable cross-reactivity with the heterologous peptides. T cells from B10.A4(R) (I-Ak) mice immunized with each of 18 natural variants of Th2R indicated a similar, limited, cross-reactivity. I-Ak competition assays showed that a number of peptides were unable to bind because of a single polymorphic residue. In both the human and mouse assays, analysis of the sequences of immunogenic cross-reactive and non-cross-reactive peptides suggested that the individual polymorphic residues affect the three-dimensional conformation of the peptide within the major histocompatibility complex (MHC) groove in an, as yet, unpredictable way. These observations argue that design of an epitope able to generate broad cross-reactivity is, to date, not possible. However, despite the limited cross-reactivity of the individual human T-cell lines, most of the donors had T-cell repertoires capable of recognizing all or nearly all of the variants tested, which supports a strategy using a **multivalent vaccine**.

L46 ANSWER 77 OF 162 MEDLINE on STN
1998436057. PubMed ID: 9765028. Effect of plasmid DNA on immunogenicity of HBsAg-anti-HBs complex. Qu D; Yuan Z H; He L F; Yang L; Li G D; Wen Y M. (Department of Molecular Virology, Shanghai Medical University, People's Republic of China.) Viral immunology, (1998) 11 (2) 65-72. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB Hepatitis B surface antigen (HBsAg) complexed with anti-HBs is more immunogenic than HBsAg alone in mice. This complex is usually used with alum as an adjuvant, which can enhance humoral response but inhibits cell-mediated immune responses. To improve the immunogenicity of HBsAg-anti-HBs, we immunized mice with a combination of this immunogenic complex and pCMVHBs, a plasmid encoding HBsAg, or the vector pCMV. Both plasmids enhanced the anti-HBs response induced by the immunogenic complex. We found 20 microg of plasmid or vector enhanced the anti-HBs response in all mice, whereas 1 microg was less effective. Splenocytes from different immunized groups were stimulated with HBsAg in vitro, and the highest level of IL-2 detected in the supernatant was found in mice immunized with HBsAg-anti-HBs plus pCMVHBs. A plasmid (pcDNA3c191) encoding core protein of hepatitis C virus (HCV) was used as an adjuvant to the immunogenic complex. A preliminary result showed that pcDNA3c191 not only enhanced the immunogenicity of HBsAg-anti-HBs, but also induced anti-HCV core antibodies. Immunization using a plasmid DNA encoding one viral antigen in combination with antigen and antibody complex of another microbial origin could be a new approach to the development of

multivalent vaccines.

L46 ANSWER 78 OF 162 MEDLINE on STN
1998269936. PubMed ID: 9607053. Adjuvant/carrier activity of inactivated tick-borne encephalitis virus. Leibl H; Tomasits R; Eibl M M; Mannhalter J W. (Department of Immunological Research, Immuno AG, Vienna, Austria.) Vaccine, (1998 Feb) 16 (4) 340-5. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Virus-like or virus-derived particles have been reported to increase the immunogenicity of foreign antigens. In this study formaldehyde-inactivated tick-borne encephalitis virus (TBEV), a potent immunogen in humans, was tested for possible adjuvant/carrier function. The results of our study revealed that substantial antibody titers against very low doses of tetanus toxoid could be obtained when mice were immunized with the antigen covalently coupled to TBEV (using N-succinimidyl-3-(2-pyridyldithio)propionate, a heterobifunctional, cleavable crosslinker containing a disulfide bridge). In contrast, only moderate anti-tetanus toxoid titers were induced by immunizations with a simple mixture of low dose tetanus toxoid and TBEV or when the disulfide bridge of the crosslinker used to couple tetanus toxoid to TBEV was cleaved prior to immunization. The antibody response to TBEV, on the other hand, was not influenced by its linkage to tetanus toxoid. Comparable anti-TBEV titers were obtained following immunization of the animals with either the TBEV-tetanus toxoid conjugate or the mixture of tetanus toxoid and TBEV. Prior application of a TBEV vaccine did not change the antibody response against tetanus toxoid and thus carrier-induced epitopic suppression could be ruled out. The abovementioned adjuvant/carrier properties of TBEV might make it a suitable candidate for use in bi- or **multivalent vaccines** containing weak immunogens.

L46 ANSWER 79 OF 162 MEDLINE on STN
1998268324. PubMed ID: 9607308. Intragenic recombinations in rotaviruses. Suzuki Y; Gojobori T; Nakagomi O. (Department of Microbiology, Akita University School of Medicine, Japan.) FEBS letters, (1998 May 8) 427 (2) 183-7. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB In this paper, evidence for intragenic recombination in the VP7 gene between rotavirus strains bearing different serotypes is demonstrated for the first time. Intragenic recombination may be one of the escaping mechanisms from the host immune system for rotavirus. This process involves exchanging antigenic regions, thus questioning the use of **multivalent vaccines** for the prevention of rotavirus infection.

L46 ANSWER 80 OF 162 MEDLINE on STN
1998239770. PubMed ID: 9572737. Chaos, persistence, and evolution of strain structure in antigenically diverse infectious agents. Gupta S; Ferguson N; Anderson R. (Wellcome Trust Centre for the Epidemiology of Infectious Disease, Zoology Department, University of Oxford, South Parks Road, Oxford OX1 3PS, UK.. sunetra.gupta@zoology.ox.ac.uk) . Science, (1998 May 8) 280 (5365) 912-5. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The effects of selection by host immune responses on transmission dynamics was analyzed in a broad class of antigenically diverse pathogens. Strong selection can cause pathogen populations to stably segregate into discrete strains with nonoverlapping antigenic repertoires. However, over a wide range of intermediate levels of selection, strain structure is unstable, varying in a manner that is either cyclical or chaotic. These results have implications for the interpretation of longitudinal epidemiological data on strain or serotype abundance, design of surveillance strategies, and the assessment of **multivalent vaccine** trials.

L46 ANSWER 81 OF 162 MEDLINE on STN
1998230920. PubMed ID: 9569464. Homologous and heterologous antibody response of cattle and sheep after vaccination with foot and mouth disease and influenza viruses. Samina I; Zakay-Rones Z; Peleg B A. (State Laboratory for Vaccine Control, Kimron Veterinary Institute, Beit Dagan,

0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Homologous and heterologous antibody response to FMD and influenza vaccines was studied in 37 calves and 45 lambs at the age of 2 months. The FMD and influenza monovalent killed vaccines were administered simultaneously twice. Another group of 18 calves was vaccinated twice, first at the age of 2 months and second at the age of 6 months, with trivalent FMD vaccine. The antibody titers were measured by ELISA and HI after second vaccination, for FMDV and influenza, respectively. The conclusions of this study are summarized as follows. Individuals, lambs and calves, that cross-respond to one heterologous serotype are liable to respond to another heterologous serotype of the same virus. Individuals, lambs and calves, showing double cross-reactivity to one virus (FMDV), are highly liable to show double cross-reactivity to entirely another virus (Influenza). **Multivalent vaccines** of FMDV are expected to elevate the antibody titers for at least one heterologous serotype (not included in the vaccine) and to detect antibodies for an additional heterologous serotype, not detected otherwise following monovalent vaccination. These results indicate the important role of the host in the spectrum of the specific immune response.

L46 ANSWER 82 OF 162 MEDLINE on STN

1998225035. PubMed ID: 9565362. Multi-plasmid DNA vaccination avoids antigenic competition and enhances immunogenicity of a poorly immunogenic plasmid. Grifantini R; Finco O; Bartolini E; Draghi M; Del Giudice G; Kocken C; Thomas A; Abrignani S; Grandi G. (Chiron Vaccines, S.p.A., Siena, Italy.) European journal of immunology, (1998 Apr) 28 (4) 1225-32. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB DNA immunization is a very promising approach to the formulation of **multivalent vaccines**. However, little information is currently available on the immunogenicity of multi-plasmid formulations. To address this issue, we immunized mice with a combination of four plasmids encoding malarial antigens and we compared antibody responses with those obtained with single-plasmid injections. We found that when four plasmids encoding Plasmodium falciparum circumsporozoite protein, thrombospondin-related anonymous protein, major merozoite surface protein (MSP)1 and Pfs25 are co-injected into mice, Ab responses against each antigen are elicited at levels at least as high as the level obtained with single-plasmid injection. The quality of antibody production, as determined by isotype analysis, was similar when single- and multi-plasmid administrations were compared, indicating the priming of the same cytokine profile for CD4+ T helper cells. The sera from mice immunized with the four-plasmid formulation specifically recognized sporozoites, blood stage schizonts and gametes, indicating that DNA immunization induced antibody responses relevant to the native conformation. Finally and of particular interest, in the case of MSP1, the antibody response appears to be strongly potentiated by the presence of additional plasmids, indicating an adjuvant effect of DNA.

L46 ANSWER 83 OF 162 MEDLINE on STN

1998128229. PubMed ID: 9467176. The humoral immune response in cattle after immunization with a multivalent IBR/PI3/Pasteurella haemolytica A1 leukotoxin vaccine. Odendaal M W; Morris S; du Preez E; Aitchison H. (Bacterial Vaccine Development Unit, Onderstepoort Veterinary Institute, South Africa.) Onderstepoort journal of veterinary research, (1997 Sep) 64 (3) 205-12. Journal code: 0401107. ISSN: 0030-2465. Pub. country: South Africa. Language: English.

AB A **multivalent vaccine** consisting of inactivated bovine herpes virus-1 (BHV-1), also known as infectious bovine rhinotracheitis virus (IBR), para-influenza type-3 virus (PI3) and the leukotoxin of Pasteurella haemolytica A1, were combined with the addition of aluminium hydroxide as adjuvant, and administered to post-weaned calves, and the serum tested for seroconversion to each antigen. Two groups of calves (n = 150 and n = 68) were used and were randomly divided into three subgroups. The first group of 150 calves were immunized with the **multivalent vaccine** (three

second group were immunized with the same vaccine 1 year later, in order to test its immunogenicity. A significant increase in titres occurred after the day 0 and 28 immunizations, for each of the three antigens in the **multivalent vaccine**, as measured on days 0 and 42. Immunoconversion occurred after immunization with the 3-month- and 1-year-old vaccine. The immunogenic stability of antigens in the vaccine was demonstrated after a 1-year period when the vaccine was kept at 4-6 degrees C.

L46 ANSWER 84 OF 162 MEDLINE on STN
97451732. PubMed ID: 9306653. **Multivalent vaccines**: prospects and challenges. Spier R E. (University of Surrey, Guildford, UK.) Folia microbiologica, (1997) 42 (2) 105-12. Ref: 17. Journal code: 0376757. ISSN: 0015-5632. Pub. country: Czech Republic. Language: English.

AB The advantages and disadvantages of combination vaccines are set out with a clear indication that, although there are many (described and discussed) influences on in the immunogenicity of a vaccine it would still be of considerable value to be able to deliver such materials with the minimum number of needle-stick injections. Such a situation may become facilitated in the future as vaccines based on plasmid DNA become available; a prospect which is examined in outline in the final section.

L46 ANSWER 85 OF 162 MEDLINE on STN
97306738. PubMed ID: 9164005. [Aseptic meningitis after mumps vaccination]. Meningites aseptiques apres vaccination anti-ourlienne. Autret E; Jonville-Bera A P; Galy-Eyraud C; Hessel L. (Pharmacologie Clinique Hopital Bretonneau, Tours, France.) Therapie, (1996 Nov-Dec) 51 (6) 681-3. Journal code: 0420544. ISSN: 0040-5957. Pub. country: ENGLAND: United Kingdom. Language: French.

AB The aim of this retrospective study was to evaluate the incidence and the characteristics of spontaneously reported aseptic meningitis (AM) in France following mumps vaccination with monovalent or **multivalent vaccines** containing the Urabe strain. Fifty-four cases of AM were reported to the regional drug surveillance centres or to the manufacturer from the time each vaccine was launched up until June 1992. Twenty cases were associated with the time off administration of a monovalent mumps vaccine and 34 with a trivalent measles, mumps and rubella vaccine (MMR). A mumps virus was isolated in four cases in the cerebrospinal fluid and an Urabe-like strain was characterised twice by polymerase chain reaction (PCR). A probable mumps origin was assumed in 17 other cases where the patients presented with other clinical or biological signs of mumps infection. The clinical outcome of AM was always favourable. The global incidence of mumps vaccine-associated AM was 0.82/100,000 doses, which is significantly lower than the incidence in the unvaccinated population. Even considering that the actual incidence of AM is much higher when assessed by active surveillance studies, the risk/benefit ratio of mumps vaccine remains in favour of vaccination. The incidence of mumps vaccines containing Jeryl Lynn (ROR Vax et Imu ORR) associated with AM needs to be evaluated.

L46 ANSWER 86 OF 162 MEDLINE on STN
97306737. PubMed ID: 9164004. [Thrombocytopenic purpura after isolated or combined vaccination against measles, mumps and rubella]. Purpura thrombopenique apres vaccination isolee ou associee contre la rougeole, la rubeole et les oreillons. Autret E; Jonville-Bera A P; Galy-Eyraud C; Hessel L. (Service de Pharmacologie Clinique, Hopital Bretonneau, Tours, France.) Therapie, (1996 Nov-Dec) 51 (6) 677-80. Journal code: 0420544. ISSN: 0040-5957. Pub. country: ENGLAND: United Kingdom. Language: French.

AB A retrospective epidemiological survey was conducted to evaluate the incidence and characteristics of thrombocytopenic purpura (TP) reported in France following measles, mumps or rubella vaccination with monovalent or **multivalent vaccines**. Sixty cases of TP were reported i.e an incidence/100,000 doses of 0.23 and 0.17 for measles or rubella vaccines respectively given alone, to 0.87 for combined measles-rubella vaccine and 0.95 for MMR vaccine. The mean age was 21 +/- 12 months and the delay of

(mean platelet count: 8000 +/- 6000/mm3) and always associated with purpura. The immediate outcome was favourable in 89.5 per cent of cases. Vaccine-associated TP appears to be similar to acute childhood idiopathic thrombocytopenic purpura but the clear temporal relationship between MMR vaccination and the occurrence of TP make a causal relationship highly plausible. Acute TP seems a rare complication of measles-rubella and MMR vaccination but clinicians had to be informed of the possibility of their occurrence. Acute TP following vaccination should be reported by physicians to their Regional Drug Surveillance Centre.

L46 ANSWER 87 OF 162 MEDLINE on STN
97261409. PubMed ID: 9107363. Humoral immune response to the 72 kDa heat shock protein from Plasmodium falciparum in populations at hypoendemic areas of malaria in western Brazilian Amazon. Alexandre C O; Camargo L M; Mattei D; Ferreira M U; Katzin A M; Camargo E P; da Silva L H. (Departmento de Parasitologia, Universidade de Sao Paulo, Brazil.) Acta tropica, (1997 Apr 15) 64 (3-4) 155-66. Journal code: 0370374. ISSN: 0001-706X. Pub. country: Netherlands. Language: English.

AB The heat-shock protein Pf72/Hsp70-1 from the human malaria parasite Plasmodium falciparum has been suggested as a potential candidate antigen for a **multivalent vaccine**. We have investigated the prevalence and levels of IgG antibodies to the recombinant protein PfR44, derived from Pf72/Hsp70-1, in individuals from different age groups living in Candeias do Jamari, an Amazonian town characterized by unstable and hypoendemic malaria transmission. Blood were collected from a household-based random sample comprising 241 people and the sera were comparatively tested against recombinant antigen PfR44 and a detergent-soluble extract of P. falciparum (PfAg-T). The prevalence and levels of IgG antibodies to both recombinant and total P. falciparum antigens were positively correlated with cumulative exposure to malaria, as estimated by the age of the individuals and the duration of their stay in the study area. Nevertheless, correlations between antibody responses to Pf72/Hsp70-1 and the acquisition of protective anti-malarial immunity could not be derived from our data.

L46 ANSWER 88 OF 162 MEDLINE on STN
97142858. PubMed ID: 8988880. Novel viral vaccines for livestock. Babiuk L A; van Drunen Littel-van den Hurk S; Tikoo S K; Lewis P J; Liang X. (Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Canada.) Veterinary immunology and immunopathology, (1996 Nov) 54 (1-4) 355-63. Ref: 49. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.

AB Recent advances in our understanding of virulence factors of viruses and the proteins or glycoproteins involved in inducing neutralizing antibodies or cell mediated immunity are forming the foundation for the development of a new generation of viral vaccines. Using bovine herpesvirus as an example, we have identified glycoproteins gB, gC, and gD as important targets for inducing neutralizing antibody responses, with gD being able to induce the highest neutralizing and cellular responses. For subunit vaccine development, the glycoproteins were produced in both prokaryotic and eukaryotic expression systems. Glycoproteins produced in eukaryotic systems were very effective in stimulating a broad range of immune responses in cattle. These glycoproteins were then formulated into effective vaccines that prevented both virus shedding and clinical disease. Herpesviruses also served as an excellent model for the identification and deletion of specific genes which lead to attenuation. In herpesviruses, two major classes of genes can be deleted. Class I includes glycoprotein genes that are nonessential for virus replication in vitro, and Class II includes genes involved in nucleic acid metabolism. these gene deleted regions can then be replaced with genes coding for protective antigens of other pathogens to develop **multivalent vaccines** in a single vector. Similar approaches are being used for other viruses including vaccinia virus and adenovirus. Finally, we introduced plasmids coding for protective antigens, gB, gC, and gD, into animals and developed immunity to these antigens. This approach has the potential to

revolutionize vaccination regimes of the future.

L46 ANSWER 89 OF 162 MEDLINE on STN
97142846. PubMed ID: 8988868. Immunobiology of pseudorabies (Aujeszky's disease). Mettenleiter T C. (Institute of Molecular and Cellular Virology, Friedrich-Loeffler-Institutes, Federal Research Centre for Virus Diseases of Animals, Insel Riems, Germany.) Veterinary immunology and immunopathology, (1996 Nov) 54 (1-4) 221-9. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.

AB Aujeszky's Disease (AD), a serious illness of pigs causing significant economic losses in the pig industry, is caused by Pseudorabies Virus (PrV). PrV belongs to the alphaherpesvirus subfamily of the herpesviruses with a double-stranded DNA genome in an enveloped capsid capable of encoding approximately 70 proteins. For disease control, vaccination with live and killed vaccines is performed. Recently, 'marked' vaccines have become available for use in eradication programs based on the differentiation between infected and vaccinated animals. PrV is also used as a viral vector for the development of **multivalent vaccines**. Despite the effectiveness of PrV vaccines, relatively little is known about the immune response against PrV infection. Several viral envelope glycoproteins have been shown to represent targets for antibody responses, and a number of isolated glycoproteins as well as genetically engineered proteins were able to elicit protective immunity. The nature of the cellular immune response is even less defined. Using viral mutants genetically engineered to lack specific antigens, it has been shown that glycoprotein C (gC) acts as a target for cytotoxic T-lymphocytes, and gB, gC, gD, and gH appear to be involved in stimulation of in vitro proliferation of PBMC from immune animals. In addition, gB and gC have been implicated in recognition of infected cells by lymphokine-activated killer (LAK) cells. In summary, the data indicate a prominent role for viral envelope glycoproteins in eliciting humoral and cellular immune responses in the animal host. A complicating factor is the ability of PrV to productively infect cells of the hematopoietic system, which may impair immune responses and might also play a role in persistent or latent infection.

L46 ANSWER 90 OF 162 MEDLINE on STN
97088750. PubMed ID: 8934658. Manipulation of the helper T cell response to influence antigenic competition occurring with a **multivalent vaccine**. Hunt J D; Brown L E; Wood P R; Stewart D J; Jackson D C. (Department of Microbiology, University of Melbourne, Australia.) Immunology and cell biology, (1996 Feb) 74 (1) 81-9. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB The reduction in antibody observed following inoculation with multiple heterologous Dichelobacter nodosus pili antigens is thought to be due to competition between antigen-specific B cells for a limited amount of T cell help. We demonstrate here that this competition is not further influenced by the expansion of cross-reactive antibody secreting cells at the expense of serogroup specific antibody secreting cells. The T cell determinants of pili recognized by sheep and BALB/c mice have been defined using 15 residue peptides. These T cell determinants include cross-reactive determinants in the conserved amino terminal region of the antigen. Here we investigate the effect of expanding the pili-specific T cell population by priming with pili derived T cell determinants. It was not possible to increase the antibody elicited in response to the **multivalent vaccine** by priming mice with either a synthetic peptide spanning a T cell determinant or with reduced and alkylated or heterologous serogroups of pili 4 weeks before inoculation with the **multivalent vaccine**. A strategy designed to increase the T cell population by inoculating animals with pili covalently coupled to an extrinsic T cell determinant was pursued.

L46 ANSWER 91 OF 162 MEDLINE on STN
97071924. PubMed ID: 8914769. Monoclonal antibodies to surface-exposes proteins of Mycoplasma mycoides subsp. mycoides (small-colony strain), which causes contagious bovine pleuropneumonia. Kiarie M N; Rurangirwa F

Microbiology and Pathology, Washington State University, Pullman 99164-7040, USA.) Clinical and diagnostic laboratory immunology, (1996 Nov) 3 (6) 746-52. Journal code: 9421292. ISSN: 1071-412X. Pub. country: United States. Language: English.

AB Outbreaks of bovine pleuropneumonia caused by small-colony strains of Mycoplasma mycoides subsp. mycoides occur in Africa, and vaccination is used for control. Since protein subunits are needed to improve **multivalent vaccines**, monoclonal antibodies (MAbs) were made to facilitate protein identification and isolation. Eleven immunoglobulin M MAbs derived from mouse spleen donors immunized with disrupted whole organisms bound periodate-sensitive epitopes on externally exposed polysaccharide. Seven of these MAbs caused in vitro growth inhibition of M. mycoides subsp. mycoides; however, reaction with carbohydrate epitopes prevented their use in identifying proteins. Ten additional MAbs from mouse spleen donors immunized with Triton X-114-phase integral membrane proteins reacted with periodate-insensitive, proteinase K-sensitive epitopes. These MAbs were classified into three groups based on immunoblots of Triton X-114-phase proteins. One group reacted with 96-, 16-, and 15-kDa proteins. Another group reacted with 26-, 21-, and 16-kDa proteins, while a third group reacted only with 26- and 21-kDa proteins. One MAb from each group reacted with trypsinsensitive epitopes on live organisms, yet none caused in vitro growth inhibition. Representative MAbs reacted with all small-colony strains in immunoblots and did not react with large colony strains. However, these MAbs were not specific for small-colony strains, as proteins from two other M. mycoides cluster organisms were identified. Nevertheless, MAbs to surface-exposed epitopes on integral membrane proteins will be useful for isolation of these proteins for immunization, since one or more might induce growth-inhibiting antibodies or other protective responses.

L46 ANSWER 92 OF 162 MEDLINE on STN

97033356. PubMed ID: 8879103. Cross-reactivity of Shigella flexneri serotype 2a O antigen antibodies following immunization or infection. Van De Verg L L; Bendiuk N O; Kotloff K; Marsh M M; Ruckert J L; Puryear J L; Taylor D N; Hartman A B. (Department of Enteric Infections, Walter Reed Army Institute of Research, Washington DC 20307-5100, USA.) Vaccine, (1996 Aug) 14 (11) 1062-8. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB To study the cross-reactivity pattern of Shigella flexneri 2a O-antigen antibodies, sera from humans and monkeys challenged with S. flexneri 2a, and from humans and guinea pigs immunized with a recombinant vaccine expressing serotype 2a O-antigen, were tested against a panel of lipopolysaccharide extracted from heterologous S. flexneri. Sera from the two groups of humans, who were volunteers in either a clinical challenge or vaccination study, showed similar patterns: cross-reactivity was more often seen with IgA antibodies, and these were mostly cross-reactive with serotype 2b, which shares the type II antigen, and serotypes 1a, 5a, and Y, which share 4 or 3, 4 group antigen, with 2a. The majority of sera from immunized guinea pigs showed both IgG and IgA cross-reactivity with 1a, 5a, and Y, but not 2b. The majority of sera from challenged monkeys showed cross-reactivity with almost all flexneri serotypes tested, with 1a, 2b, and Y being recognized most often, and the cross-reactive antibodies were more often IgG than IgA. These results show that either immunization or challenge with the 2a serotype induces cross-reactive antibodies which recognize similar subsets of heterologous serotypes, and suggest that it may be possible to design **multivalent vaccines** against S. flexneri.

L46 ANSWER 93 OF 162 MEDLINE on STN

97018844. PubMed ID: 8865460. Hepatitis C virus: biological and clinical consequences of genetic heterogeneity. Cooreman M P; Schoondermark-Van de Ven E M. (Dept. of Gastroenterology and Hepatology, University Hospital St. Radboud, Nijmegen, The Netherlands.) Scandinavian journal of gastroenterology. Supplement, (1996) 218 106-15. Ref: 86. Journal code: 0437034. ISSN: 0085-5928. Pub. country: Norway. Language: English.

and sporadic hepatitis. In Western Europe, anti-HCV is detected in 0.4-1.5% of healthy blood donors. There is a high frequency of progressive chronic hepatitis, ranging from 50 to 80%, which leads to cirrhosis in 20-50% of patients after 10-20 years. Viremic patients with minimal biochemical abnormalities may have chronic liver disease histologically. There is growing evidence that virological features of HCV are associated with different clinical manifestations and response to therapy. The RNA genome consists of a 5' and 3' Untranslated Region, a structural domain encoding the core and envelope proteins, and a non-structural domain. Different HCV isolates show a high sequence heterogeneity, which has led to the classification of currently six genotypes and several subtypes. There is a marked difference in the geographic distribution of HCV genotypes, with types 1, 2 and 3a being most frequently found in western countries. In The Netherlands, subtype 1b accounts for approximately 60% of all cases of chronic HCV. Serologic diagnosis based on recombinant C-100 antigens (first generation immunoassays) only reliably detected type 1, due to the heterogeneity of the NS4 region; inclusion of more conserved proteins c22 and c33 (second generation assays) has largely improved sensitivity of anti-HCV testing. Genotype 1b is associated with more severe liver disease and with lower response rates for antiviral therapy, compared with types 2 and 3. Quasispecies nature and escape mutants may enable viral persistence and the development of chronic liver disease. As cross-reactivity between genotypes is unlikely, prevention of HCV disease may be dependent on the development of **multivalent vaccines**.

L46 ANSWER 94 OF 162 MEDLINE on STN

97000543. PubMed ID: 8843628. Oral immunization with recombinant Salmonella typhimurium expressing surface protein antigen A (SpaA) of Streptococcus sobrinus: effects of the Salmonella virulence plasmid on the induction of protective and sustained humoral responses in rats. Redman T K; Harmon C C; Michalek S M. (Department of Microbiology, University of Alabama at Birmingham 35294-2170, USA.) Vaccine, (1996 Jun) 14 (9) 868-78. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Recombinant strains of Salmonella typhimurium have been studied as antigen delivery systems to determine their effectiveness as **multivalent vaccines**. Here we compare the efficacy of two strains of S. typhimurium. chi 4072 (pYA2905) and chi 3987 (pYA2905), expressing SpaA of Streptococcus sobrinus 6715 as oral vaccines for dental caries. Both strains are attenuated delta cya delta crp delta asd mutants with their Asd phenotypes complemented by the Asd+ plasmid pYA2905, which also encodes a peptide fragment of SpaA. S. typhimurium chi 3987 (pYA2905), unlike S. typhimurium chi 4072 (pYA2905), contains the 100 kb S. typhimurium virulence plasmid. Fischer rats were orally immunized with approximately 10(9) S. typhimurium chi 3987 (pYA2905) or chi 4072 (pYA2905) and then challenged with cariogenic S. sobrinus 6715. Rats orally immunized with either strain of recombinant Salmonella developed salivary IgA anti-SpaA responses and had lower levels of S. sobrinus-induced dental caries than nonimmunized, infected animals. In a second series of experiments, the kinetics and isotype of the serum and salivary antibody responses were determined in rats orally immunized with S. typhimurium chi 3987 (pYA2905) or chi 4072 (pYA2905) on weeks 0 and 8. IgG and IgM serum antibody responses to SpaA and S. typhimurium were detected after the primary and secondary immunizations, and the secondary immunization boosted serum IgG anti-Salmonella activity. In general, animals immunized with chi 3987 (pYA2905) had higher serum anti-SpaA, as well as serum and salivary anti-Salmonella, responses than animals immunized with chi 4072 (pYA2905). This study demonstrates the effective use of two recombinant S. typhimurium strains as oral vaccines for inducing protective and sustained immune responses against a mucosal pathogen and suggests that the recombinant Salmonella vaccine strain carrying the virulence plasmid induced similar or higher protective immune responses than the strain lacking the virulence plasmid.

96417858. PubMed ID: 8820649. A Salmonella typhimurium htrA live vaccine expressing multiple copies of a peptide comprising amino acids 8-23 of herpes simplex virus glycoprotein D as a genetic fusion to tetanus toxin fragment C protects mice from herpes simplex virus infection. Chabalgoity J A; Khan C M; Nash A A; Hormaeche C E. (Department of Microbiology, University of Newcastle, Newcastle upon Tyne, UK.) Molecular microbiology, (1996 Feb) 19 (4) 791-801. Journal code: 8712028. ISSN: 0950-382X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Multiple tandem copies of an immunogenic epitope comprising amino acids 8-23 of glycoprotein D of herpes simplex virus (HSV) were expressed as C-terminal fusions to tetanus toxin fragment C (TetC) in different Salmonella typhimurium live vaccine strains. Expression of the longer fusions was best in strains harbouring a lesion in htrA, a stress protein gene. SL3261, an aroA strain, did not effectively express the longer fusions. Mice immunised with an S. typhimurium C5 htrA mutant expressing fusions with two or four copies of the peptide made an antibody response to both the peptide and TetC, whereas constructs expressing one copy of the peptide only elicited antibody to TetC. A non-immunogenic octameric fusion underwent rearrangements in vivo resulting in a predominantly monomeric fusion. In contrast, the S. typhimurium SL3261 aroA vaccine expressing the TetC-tetrameric fusion did not elicit antibody to the peptide. Sera from mice immunised with a single dose of the dimer and tetramer fusions in the htrA strain neutralised HSV in vitro, and the mice were protected from HSV infection as measured by a reduction in virus load in the ear pinna. We have previously shown that mice vaccinated with salmonella expressing TetC are protected against tetanus toxin and virulent salmonella challenge. These results suggest that it may be possible to develop a **multivalent vaccine** against salmonellosis, tetanus and HSV.

L46 ANSWER 96 OF 162 MEDLINE on STN

96405329. PubMed ID: 8809469. Rotavirus vaccines: an overview. Midthun K; Kapikian A Z. (Division of Vaccines and Related Products Application, Food and Drug Administration, Rockville, Maryland 20852, USA.) Clinical microbiology reviews, (1996 Jul) 9 (3) 423-34. Ref: 153. Journal code: 8807282. ISSN: 0893-8512. Pub. country: United States. Language: English.

AB Rotavirus vaccine development has focused on the delivery of live attenuated rotavirus strains by the oral route. The initial "Jennerian" approach involving bovine (RIT4237, WC3) or rhesus (RRV) rotavirus vaccine candidates showed that these vaccines were safe, well tolerated, and immunogenic but induced highly variable rates of protection against rotavirus diarrhea. The goal of a rotavirus vaccine is to prevent severe illness that can lead to dehydration in infants and young children in both developed and developing countries. These studies led to the concept that a **multivalent vaccine** that represented each of the four epidemiologically important VP7 serotypes might be necessary to induce protection in young infants, the target population for vaccination. Human-animal rotavirus reassortants whose gene encoding VP7 was derived from their human rotavirus parent but whose remaining genes were derived from the animal rotavirus parent were developed as vaccine candidates. The greatest experience with a **multivalent vaccine** to date has been gained with the quadrivalent preparation containing RRV (VP7 serotype 3) and human-RRV reassortants of VP7 serotype 1, 2, and 4 specificity. Preliminary efficacy trial results in the United States have been promising, whereas a study in Peru has shown only limited protection. Human-bovine reassortant vaccines, including a candidate that contains the VP4 gene of a human rotavirus (VP4 serotype 1A), are also being studied.

L46 ANSWER 97 OF 162 MEDLINE on STN

96363703. PubMed ID: 8719515. Immunological parameters associated with antigenic competition in a multivalent footrot vaccine. Hunt J D; Jackson D C; Wood P R; Stewart D J; Brown L E. (Department of Microbiology, University of Melbourne, Parkville, Victoria, Australia.) Vaccine, (1995 Dec) 13 (17) 1649-57. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A murine model for antigenic competition with multivalent N. nodosus pili
vaccine has been established that parallels the phenomenon observed in sheep where levels of antibody, specific for any particular serogroup of pili, are significantly lower following vaccination in the presence of multiple serogroups of pili than with that serogroup alone. This competition was observed in both high and low responder strains of mice and was not dependent on the multiplicity of the antigens in the **multivalent vaccine** but could be observed with a large excess of a single heterologous serogroup. Competition was manifest by a reduction in the number of serogroup-specific antibody secreting cells elicited in response to vaccination. The antibody response to a single serogroup of pili reached a plateau at high doses and it was at these doses that antigenic competition was most pronounced, under conditions where both B- and T-cell responses were limiting. The limit in T-cell responsiveness was not imposed at the level of presentation of antigen. Pili-specific T cells were largely cross-reactive for different serogroups, and under conditions of limiting T-cell stimulation within a lymph node the available T cells would have to be shared between B cells specific for each serogroup of pili, which may in turn result in the decrease of serogroup-specific antibody induced following inoculation with the **multivalent vaccine**.

L46 ANSWER 98 OF 162 MEDLINE on STN
96355051. PubMed ID: 8752300. Selected regulatory and scientific topics for candidate rotavirus vaccine development. Henchal L S; Midthun K; Goldenthal K L. (Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Research and Review, Food and Drug Administration, Rockville, Maryland, USA.) Journal of infectious diseases, (1996 Sep) 174 Suppl 1 S112-7. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Various aspects of the development of rotavirus vaccine candidates are discussed. As is true with other vaccines, comprehensive testing must be done to detect the possible presence of adventitious agents in the vaccine and seed preparations. Consideration must also be given to other biologic materials that come in contact with the vaccine preparation during production to prevent the introduction of contaminants. The clinical testing of rotavirus vaccines from early safety and immunogenicity studies through final efficacy studies is also discussed. Issues surrounding coadministration of investigational rotavirus vaccines with US-licensed vaccines are ideally addressed before initiation of efficacy trials. Other subjects discussed are identification of correlates of protection, **multivalent vaccines**, foreign efficacy trials, safety data, and statistical considerations. Sponsors of investigational vaccines are urged to contact the Food and Drug Administration for guidance during the development process, especially before the investigational new drug application and pivotal efficacy trial stages.

L46 ANSWER 99 OF 162 MEDLINE on STN
96331999. PubMed ID: 8731940. Construction of shuttle expression plasmid and stable expression of foreign gene in mycobacteria and E. coli. Huangfu Y M; Zhang D J; Cheng J Z; Qian M; Liang J Q; Li D. (Department of Medical Molecular Biology, Tongji Medical University, Wuhan.) Journal of Tongji Medical University = T'ung chi i k'o ta hsueh hsueh pao, (1995) 15 (3) 138-42. Journal code: 8605495. ISSN: 0257-716X. Pub. country: China. Language: English.

AB By employing the pUC19 as a backbone, the regulatory and signal sequences which encode kanamycin resistance, and mycobacterial plasmid origin of replication (oriM) were cloned into the pUC19. The recombinant E. Coli-mycobacteria shuttle expression plasmid pBCG-8000 was constructed. The pBCG-8000 was able to replicate in both E. Coli and mycobacteria (including BCG) systems, and to confer stable kanamycin resistance upon transformants. The study should facilitate the development of BCG and other mycobacteria into **multivalent vaccine** vectors.

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L46 ANSWER 50 OF 162 MEDLINE on STN
2001248118. PubMed ID: 11292735. Attenuated Shigella flexneri 2a Delta guaBA strain CVD 1204 expressing enterotoxigenic Escherichia coli (ETEC) CS2 and CS3 fimbriae as a live mucosal vaccine against Shigella and ETEC infection. Altboum Z; Barry E M; Losonsky G; Galen J E; Levine M M. (Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.) Infection and immunity, (2001 May) 69 (5) 3150-8. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB To construct a prototype hybrid vaccine against Shigella and enterotoxigenic Escherichia coli (ETEC), the genes encoding the production of ETEC CS2 and CS3 fimbriae were isolated and expressed in attenuated Shigella flexneri 2a guaBA strain CVD 1204. The CS2 cotA to -D genes, isolated from ETEC strain C91F, and the CS3 cstA to -H genes, subcloned from plasmid pCS100, were cloned into 15-copy-number-stabilized pGA1 behind the osmotically regulated ompC promoter, resulting in high expression of both fimbriae. Under nonselective in vitro growth conditions, pGA1-CS2 and pGA1-CS3 were stable in CVD 1204, exhibiting a plasmid loss of only approximately 1% per duplication. Expression of CS2 and CS3 reduced the invasiveness of Shigella for HeLa cells and slowed the intracellular growth rate. Guinea pigs immunized intranasally with CVD 1204(pGA1-CS2) or CVD 1204(pGA1-CS3), or with a mixture of these strains, developed secretory immunoglobulin A (IgA) in tears and serum IgG antibodies against Shigella lipopolysaccharide, CS2, and CS3 antigens. Moreover, the animals were protected against keratoconjunctivitis following conjunctival challenge with virulent S. flexneri 2a strain 2457T. Animals immunized with Shigella expressing CS2 or CS3 developed serum antibodies that agglutinated Shigella as well as an ETEC strain bearing the homologous fimbriae, whereas animals immunized with combined CVD 1204(pGA1-CS2) and CVD 1204(pGA1-CS3) developed antibodies that agglutinated all three test strains. These observations support the feasibility of a **multivalent vaccine** against shigellosis and ETEC diarrhea consisting of multiple Shigella live vectors expressing relevant ETEC antigens.

L46 ANSWER 51 OF 162 MEDLINE on STN
2001232832. PubMed ID: 11214239. Characterization of aluminium-containing adjuvants. White J L; Hem S L. (Department of Agronomy, Purdue University, West Lafayette, IN 47907-1150, USA.) Developments in biologicals, (2000) 103 217-28. Journal code: 100940058. ISSN: 1424-6074. Pub. country: Switzerland. Language: English.

AB The approved aluminium-containing vaccine adjuvants have been shown to be poorly crystalline aluminium oxyhydroxide (AIO(OH)) and amorphous aluminium hydroxyphosphate of varying phosphate content. Adsorption of the antigen by the adjuvant is implied in many proposed mechanisms of antibody production enhancement caused by the adjuvants. The World Health Organization recommends adsorption of 80% or more of tetanus and diphtheria toxoid by the aluminium-containing adjuvants. Thus, one objective in the preparation of vaccines containing these adjuvants is to optimize adsorption of the antigen on the adjuvant. Production of a consistent adjuvant effect in vaccines would be facilitated by the thorough characterization of aluminium-containing adjuvants with reference to properties that affect adsorption and other colloidal behaviour. Such properties include surface area, surface charge, chemical composition, structure, and morphology. Techniques and measurements such as X-ray diffraction, infrared spectroscopy, transmission electron microscopy, energy-dispersive spectrometry, Doppler electrophoretic light scattering analysis, dissolution rates, and adsorption isotherms provide a basis for understanding and predicting interactions and behaviour in monovalent as well as **multivalent vaccines**. Such characterization would be crucial in vaccine standardization and quality control.

L46 ANSWER 52 OF 162 MEDLINE on STN
2001232822. PubMed ID: 11214229. Simultaneous evaluation of molecular size and antigenic stability of PNEUMOVAX 23, a multivalent pneumococcal

polysaccharide vaccine. Sweeney J A; Summer J S; Hennessey J P Jr.
(Bioprocess and Bioanalytical Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA 19486-0004, USA.) Developments in biologicals, (2000) 103 11-26. Journal code: 100940058. ISSN: 1424-6074. Pub. country: Switzerland. Language: English.

AB A technique using high performance size exclusion chromatography (HPSEC) with rate nephelometry (RN) detection has been developed to simultaneously measure the relative molecular size and antigenicity of the bacterial polysaccharide components in a multivalent pneumococcal vaccine, PNEUMOVAX 23. This assay was used to establish stability profiles for each of the 23 pneumococcal polysaccharide serotypes in this vaccine formulation, based on concurrent analyses of vaccine lots up to nine years of age. The exceptional inter-assay precision (<1% RSD) permitted detailed analysis of the data and a more accurate measure of the stability of this product that heretofore has not been available. While 21 of the 23 serotypes in the vaccine show essentially no change in molecular size over several years, serotypes 19A and 19F show changes in relative molecular size of approximately 2% per year. Similar decreases in relative molecular size for serotypes 19A and 19F stored in aqueous formulation have also been observed in other commercially available pneumococcal vaccine products. Additionally, stability profiles of relative antigenicity for nine of the 23 serotypes are reported based on information that is simultaneously obtained in the HPSEC/RN analysis. Of the nine serotypes examined, only serotypes 1, 9V and 18C demonstrate antigenic lability over time, in each case showing a decrease in antigenicity on the order of 5% to 10% per year. Overall, this method is a precise and efficient means of providing data on relative molecular size and relative antigenicity for each polysaccharide component of a **multivalent vaccine** product. Application of this method in stability studies of such vaccines provides critical information for evaluating time-dependent changes in these products.

L46 ANSWER 53 OF 162 MEDLINE on STN
2001089478. PubMed ID: 11137236. Infant and adolescent hepatitis B immunization up to 1999: a global overview. Vryheid R E; Kane M A; Muller N; Schatz G C; Bezabeh S. Vaccine, (2000 Dec 8) 19 (9-10) 1026-37. Ref: 130. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This article presents a global overview of hepatitis B infant and adolescent immunization programmes. The 108 reported universal infant or adolescent immunization programmes and 87 reported national infant coverage rates fit a pattern, explained by hepatitis B endemicity, prosperity, policy emphasis, and immunization programme strength. Most East and Southeast Asian, Pacific, and Middle Eastern countries have intermediate to highly endemic hepatitis B. Most have achieved 65-100% coverage. South and Central Asia and sub-Saharan Africa have intermediate to high endemicity, with some countries having hepatitis B immunization programmes. Some Southern and Eastern European countries, with intermediate endemicity, have high coverage. Low endemic Northern European countries vaccinate higher risk groups; some have universal infant or adolescent programmes. Caribbean and Latin American countries have varying endemicity, and most started programmes. Low endemic North American countries have universal vaccination programmes. Universal immunization strategies have greatly reduced incidence and prevalence, and are cost-effective for many countries, but many have difficulties affording this vaccine. Globally, most infants are not being immunized against hepatitis B virus infection. Increasing coverage, and decreasing the numbers of people diseased and dying from this virus, may require delivering heat-stable vaccine beyond cold chains, creative financing to reduce prices, and **multivalent vaccines**.

L46 ANSWER 54 OF 162 MEDLINE on STN
2001038345. PubMed ID: 10970378. Distribution of Neisseria meningitidis serogroup B serosubtypes and serotypes circulating in the United States. The Active Bacterial Core Surveillance Team. Tondella M L; Popovic T; Rosenstein N E; Lake D B; Carlone G M; Mayer L W; Perkins B A. (Meningitis

and Special Pathogens Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA.. MLT5@CDC.GOV) . Journal of clinical microbiology, (2000 Sep) 38 (9) 3323-8. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB Because the Neisseria meningitidis serogroup B (NMSB) capsule is poorly immunogenic in humans, immunization strategies have focused on noncapsular antigens. Both PorA and to a lesser extent PorB are noncapsular protein antigens capable of inducing protective bactericidal antibodies, and vaccines based on the outer membrane protein (OMP) components of serogroup B meningococci have been shown to be effective in clinical trials. Multiple PorA antigens seem to be needed to prevent endemic meningococcal disease around the world, and a hexavalent PorA-based meningococcal vaccine has recently been developed in The Netherlands. To evaluate the distribution of NMSB PorA and PorB antigens in the United States, serosubtyping and serotyping were done on 444 NMSB strains isolated in the active surveillance areas of the United States (total population, 32 million) during the period 1992 to 1998. A total of 244 strains were isolated from sporadic cases of meningococcal disease, and 200 strains were isolated from an epidemic in Oregon. A panel of 16 mouse monoclonal antibodies reactive with PorA and 15 monoclonal antibodies reactive with PorB were used. Among the NMSB isolates obtained from sporadic cases, the most prevalent serosubtypes were P1.7,16 (14.3%), P1.19,15 (9.8%), P1.7,1 (8.6%), P1.5,2 (7.8%), P1. 22a, 14 (7.8%), and P1.14 (5.3%) and the most prevalent serotypes were 4,7 (27.5%), 15 (16%), 14 (8.6%), 10 (6.1%), 1 (4.9%), and 2a (3.7%). A multivalent PorA-based OMP vaccine aimed at the six most prevalent serosubtypes could have targeted about half of the sporadic cases of NMSB disease that occurred between 1992 and 1998 in the surveillance areas. Twenty serosubtypes would have had to be included in a **multivalent vaccine** to achieve 80% coverage of strains causing sporadic disease. The relatively large number of isolates that did not react with murine monoclonal antibodies indicates that DNA sequence-based variable region typing of NMSB will be necessary to provide precise information on the distribution and diversity of PorA antigens and correlation with nonserosubtypeable isolates. The high degree of variability observed in the PorA and PorB proteins of NMSB in the United States suggests that vaccine strategies not based on OMPs should be further investigated.

L46 ANSWER 55 OF 162 MEDLINE on STN

2000494779. PubMed ID: 10967218. Recent advances in the use of DNA vaccines for the treatment of diseases of farmed animals. van Drunen Littel-van den Hurk S; Gerdts V; Loehr B I; Pontarollo R; Rankin R; Uwiera R; Babiuk L A. (Veterinary Infectious Disease Organization, 120 Veterinary Road, Saskatoon, Saskatchewan S7N 5E3, Canada.) Advanced drug delivery reviews, (2000 Sep 15) 43 (1) 13-28. Ref: 70. Journal code: 8710523. ISSN: 0169-409X. Pub. country: Netherlands. Language: English.

AB DNA-based vaccination constitutes one of the most recent approaches to vaccine development. This technology is in principle one of the most simple and yet versatile methods of inducing both humoral and cellular immune responses, as well as protection against a variety of infectious agents. However, although immune responses have been induced in a number of larger species, most information on the efficacy of DNA immunization has been generated in mice. In this review the information available to date about the use of DNA vaccines in farmed animals, including cattle, pigs and poultry, is presented. The areas that need specific attention in the future to bring this technology to the market are discussed, including the issues concerning delivery, safety, compatibility of plasmids in **multivalent vaccines** and the potential of using immune stimulants as part of a DNA vaccine.

L46 ANSWER 56 OF 162 MEDLINE on STN

2000464360. PubMed ID: 11016226. [WHO spearheads global initiative to eradicate hepatitis B]. WHO leder globalt initiativ for att utrota hepatit B. Sylvan S. (Karolinska sjukhuset, Stockholm.. staffan.sylvan@sme.sll.se) . Lakartidningen, (2000 Aug 30) 97 (35)

Language: Swedish.

AB It is estimated that over 350 million people live with a chronic hepatitis B virus (HBV) infection, claiming over one million deaths per year due to progress of the chronic disease to cirrhosis and/or hepatocellular carcinoma (HCC). An extended program of immunization including hepatitis B vaccine for children under one year of age has been launched in more than 110 countries. Recent studies conclude that mass hepatitis B immunization is effective in preventing HBV infection and has resulted in a decrease in the occurrence of HCC in children living in countries where hepatitis B is endemic. However, the vast majority of infected children live in the poorest developing countries in Africa and Asia that currently cannot afford the vaccine or lack the basic infrastructure necessary to deliver a national immunization service. The Global Alliance for Vaccines and Immunization (GAVI) was established in 1999 as an alliance of WHO, UNICEF, the World Bank, industry, foundations, and other partners to reinvent immunization for the 21st century, by forging a common vision and new ways of working together at global, regional and national levels. WHO recommends global elimination of hepatitis B by universal infant and/or adolescent immunization, but health planners in Sweden and the other Scandinavian countries, the Netherlands and UK have not yet been convinced of the cost-effectiveness of HB-prevention through routine childhood immunization with HB-vaccine. The inclusion of hepatitis B vaccine in already available **multivalent vaccines** may alter this situation in the future, but until then an intensified vaccination strategy aimed at those groups of individuals that are particularly at risk for hepatitis B should be adopted in accordance with the recommendations of The Swedish National Board of Health (SOSFS 1991:2) and local instructions from the County Medical Officer for Communicable Disease Control.

L46 ANSWER 57 OF 162 MEDLINE on STN

2000445464. PubMed ID: 10994510. Estimating vaccine coverage by using computer algebra. Altmann D; Altmann K. (Robert Koch Institut, Berlin, Germany.. altmannd@rki.de) . IMA journal of mathematics applied in medicine and biology, (2000 Jun) 17 (2) 137-46. Journal code: 8704892. ISSN: 0265-0746. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The approach of N Gay for estimating the coverage of a **multivalent vaccine** from antibody prevalence data in certain age cohorts is complemented by using computer aided elimination theory of variables. Hereby, Gay's usage of numerical approximation can be replaced by exact formulae which are surprisingly nice, too.

L46 ANSWER 58 OF 162 MEDLINE on STN

2000407873. PubMed ID: 10775787. Expression library immunization protects mice against a challenge with virulent rodent malaria. Smooker P M; Setiady Y Y; Rainczuk A; Spithill T W. (Department of Biochemistry and Molecular Biology, Monash University, Clayton 3800, Australia.. peter.smooker@med.monash.edu.au) . Vaccine, (2000 May 22) 18 (23) 2533-40. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Although several candidate vaccine antigens have been developed for malaria, there is as yet no effective single vaccine available. There is a growing consensus that the ultimate malaria vaccine will be multivalent, requiring the identification of a suitable cocktail of antigens. However, evaluation of the multitude of potential malaria vaccine antigens in suitable combinations is a daunting task. Here we describe the validation of expression library immunization (ELI) as a tool for the discovery of sequences protective against malaria infection. A genomic Plasmodium chabaudi expression library was constructed comprising ten separate pools of 3000 plasmids. Over three vaccine trials using biolistic delivery of pools composed of 616 to 30,000 plasmids we report up to 63% protection of mice from a challenge with P. chabaudi adami DS, a highly virulent strain. Overall, ELI protected 36% of vaccinated mice against virulent challenge compared with only 3.2% survival of control mice. These results demonstrate that ELI is a suitable approach for screening the malaria genome to identify the components of **multivalent vaccines**.

L46 ANSWER 59 OF 162 MEDLINE on STN
2000240040. PubMed ID: 10775593. Expression of an antigenic adenovirus epitope in a group B coxsackievirus. Hofling K; Tracy S; Chapman N; Kim K S; Smith Leser J. (Enterovirus Research Laboratory, Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska 68198-6495, USA.) Journal of virology, (2000 May) 74 (10) 4570-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Group B coxsackieviruses (CVB) cause human myocarditis, while human adenovirus type 2 (Ad2) is implicated as an agent of this disease. The L1 loop of the Ad2 hexon protein has been demonstrated to be antigenic in rabbits. To evaluate the feasibility of a **multivalent vaccine** strain against the CVB and Ad2, we cloned the sequence encoding the Ad2 hexon L1 loop, flanked by dissimilar sequences encoding the protease 2A (2Apro) recognition sites, into the genome of an attenuated strain of CVB type 3 (CVB3/0) at the junction of 2Apro and the capsid protein 1D. Progeny virus (CVB3-PL2-Ad2L1) was obtained following transfection of the construct into HeLa cells. Replication of CVB3-PL2-Ad2L1 in diverse cell cultures demonstrated that the yield of the chimeric virus was between 0.5 to 2 log units less than the parental strain. Western blot analyses of the CVB3 capsid protein 1D in CVB3-PL2-Ad2L1-infected HeLa cells demonstrated production of the expected capsid protein. Viral proteins were detected earlier and in approximately fourfold greater amounts in CVB3-PL2-Ad2L1-infected HeLa cells than in CVB3/0-infected cells. Cleavage of the CVB3-PL2-Ad2L1 polyprotein by 2Apro was slowed, accompanied by an accumulation of the fusion 1D-L1 loop protein. Reverse transcription-PCR sequence analysis of CVB3-PL2-Ad2L1 RNA demonstrated that the Ad2 hexon polypeptide coding sequence was maintained in the chimeric viral genome through at least 10 passages in HeLa cells. Mice inoculated with CVB3-PL2-Ad2L1 demonstrated a brief viremia with no replication detectable in the heart but prolonged replication of virus in the pancreas in the absence of pathologic changes in either organ. CVB3-PL2-Ad2L1 induced binding and neutralizing anti-Ad2 antibodies, in addition to antibodies against CVB3 in mice. CVB3-PL2-Ad2L1 was used to challenge mice previously inoculated with CVB3/0 and with preexisting anti-CVB3 neutralizing-antibody titers; anti-Ad2 neutralizing and binding antibodies were induced in these mice at higher levels than in mice without anti-CVB3 immunity. The data demonstrate that a CVB vector can stably express an antigenic polypeptide of Ad2 from within the CVB open reading frame that results in the induction of protective immune responses against both viruses.

L46 ANSWER 60 OF 162 MEDLINE on STN
2000113867. PubMed ID: 10649618. A new protocol for a challenge test to assess the efficacy of live anticoccidial vaccines for chickens. Williams R B; Catchpole J. (Schering-Plough Animal Health, Uxbridge, Middlesex, UK.) Vaccine, (2000 Jan 18) 18 (13) 1178-85. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The search for vaccines to control coccidioses caused by Eimeria species in chickens (Gallus gallus) is intensifying because of the increasing threat of drug resistance to anticoccidial agents. It is important, therefore, to develop a reliable standard method for the assessment of **multivalent vaccine** efficacy, because many criteria generally used to judge drug efficacy are not appropriate for vaccines. The lack of correlations between oocyst production, severity of lesions and bird weight gains is discussed. Furthermore, not all Eimeria species cause pathognomonic lesions. A new protocol for a vaccine efficacy test is described which uses growth rate of chickens after virulent challenge as the primary criterion and feed conversion ratio as the secondary criterion for protection against each of the separate coccidioses caused by the seven species of Eimeria that parasitize the chicken. The benefits to this protocol over previous ad hoc experimental designs are: (1) immunization is carried out with **multivalent vaccines** of Eimeria species up to the maximum of seven that may infect chickens; (2) assessments of immunity are carried out for each species separately so

results can not be confounded; (3) the criteria of efficacy are those that are crucial to demonstrate commercial usefulness; (4) the possibility of drawing erroneous conclusions based upon inappropriate criteria such as oocyst production or lesion scores is avoided; (5) because the same criteria are used for each species, direct comparisons may be made amongst immunities to all of the species in the vaccine being tested. Results are presented from tests of three commercial batches of Paracox attenuated anticoccidial vaccine, showing that separate virulent challenges with all seven Eimeria species were controlled in vaccinated chicks.

L46 ANSWER 61 OF 162 MEDLINE on STN
2000097658. PubMed ID: 10634192. Antibodies from HIV-positive and AIDS patients bind to an HIV envelope **multivalent vaccine**. Carlos M P; Yamamura Y; Diaz-Mitoma F; Torres J V. (Department of Medical Microbiology and Immunology, School of Medicine, University of California, Davis 95616, USA.) Journal of acquired immune deficiency syndromes (1999), (1999 Dec 1) 22 (4) 317-24. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB A major problem impeding development of an effective HIV vaccine is the rapid antigenic variability that is characteristic of several envelope glycoprotein epitopes. Frequent mutations alter the composition of the most immunogenic regions of the envelope glycoprotein. We have prepared a synthetic immunogen representing the evolution of the major hypervariable epitopes on the envelope glycoprotein (gp120) of HIV-1. Five synthetic constructs, representing each of the HIV-1 gp120 hypervariable epitopes were tested for recognition by antibodies from patients infected with HIV-1 from different geographic regions worldwide. An HIV-1 human plasma panel provided a representation of the antibodies recognizing subtype-specific epitope sequences prevalent at different parts of the world. The vaccine construct was recognized by antibodies from HIV-1-positive individuals infected with subtypes A, B, C, D, E, and F. Antibodies in pooled HIV-1 patient sera from San Francisco also recognized all five constructs. This complex immunogen was recognized by antibodies in sera from individual HIV-1-positive and AIDS patients from Puerto Rico and Canada, with a strong binding to the complete vaccine and the V3 component. Altogether, our results demonstrate that antibodies from seropositive patients infected with different HIV-1 clades recognize and bind to the HIV hypervariable epitope construct vaccine preparation and its individual components.

L46 ANSWER 62 OF 162 MEDLINE on STN
2000063611. PubMed ID: 10594972. DNA vaccines for viral diseases. Davis H L; McCluskie M J. (Loeb Research Institute, Ottawa Civic Hospital, 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9, Canada.) Microbes and infection / Institut Pasteur, (1999 Jan) 1 (1) 7-21. Ref: 189. Journal code: 100883508. ISSN: 1286-4579. Pub. country: France. Language: English.

AB DNA vaccines, with which the antigen is synthesized in vivo after direct introduction of its encoding sequences, offer a unique method of immunization that may overcome many of the deficits of traditional antigen-based vaccines. By virtue of the sustained in vivo antigen synthesis and the comprised stimulatory CpG motifs, plasmid DNA vaccines appear to induce strong and long-lasting humoral (antibodies) and cell-mediated (T-help, other cytokine functions and cytotoxic T cells) immune responses without the risk of infection and without boost. Other advantages over traditional antigen-containing vaccines are their low cost, the relative ease with which they are manufactured, their heat stability, the possibility of obtaining **multivalent vaccines** and the rapid development of new vaccines in response to new strains of pathogens. The antigen-encoding DNA may be in different forms and formulations, and may be introduced into cells of the body by numerous methods. To date, animal models have shown the possibility of producing effective prophylactic DNA vaccines against numerous viruses as well as other infectious pathogens. The strong cellular responses also open up the possibility of effective therapeutic DNA vaccines to treat chronic viral infections.

1999429594. PubMed ID: 10501486. Lyssavirus glycoproteins expressing immunologically potent foreign B cell and cytotoxic T lymphocyte epitopes as prototypes for **multivalent vaccines**. Desmezieres E; Jacob Y; Saron M F; Delpeyroux F; Tordo N; Perrin P. (Laboratoire des Lyssavirus, Institut Pasteur 25, Paris, France.) Journal of general virology, (1999 Sep) 80 (Pt 9) 2343-51. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Truncated and chimeric lyssavirus glycoprotein (G) genes were used to carry and express non-lyssavirus B and T cell epitopes for DNA-based immunization of mice, with the aim of developing a **multivalent vaccine** prototype. Truncated G (GPVIII) was composed of the C-terminal half (aa 253-503) of the Pasteur rabies virus (PV: genotype 1) G containing antigenic site III and the transmembrane and cytoplasmic domains. The chimeric G (GEBL1-PV) was composed of the N-terminal half (aa 1-250) of the European bat lyssavirus 1 (genotype 5) G containing antigenic site II linked to GPVIII. Antigenic sites II and III are involved in the induction of virus-neutralizing antibodies. The B cell epitope was the C3 neutralization epitope of the poliovirus type 1 capsid VP1 protein. The T cell epitope was the H2d MHC I-restricted epitope of the nucleoprotein of lymphocytic choriomeningitis virus (LCMV) involved in the induction of both cytotoxic T cell (CTL) production and protection against LCMV. Truncated G carrying foreign epitopes induced weak antibody production against rabies and polio viruses and provided weak protection against LCMV. In contrast, the chimeric plasmid containing various combinations of B and CTL epitopes elicited simultaneous immunological responses against both parental lyssaviruses and poliovirus and provided good protection against LCMV. The level of humoral and cellular immune responses depended on the order of the foreign epitopes inserted. Our results demonstrate that chimeric lyssavirus glycoproteins can be used not only to broaden the spectrum of protection against lyssaviruses, but also to express foreign B and CTL epitopes. The potential usefulness of chimeric lyssavirus glycoproteins for the development of **multivalent vaccines** against animal diseases and zoonoses, including rabies, is discussed.

L46 ANSWER 64 OF 162 MEDLINE on STN

1999416392. PubMed ID: 10486924. New chimaeric hepatitis B virus core particles carrying hantavirus (serotype Puumala) epitopes: immunogenicity and protection against virus challenge. Ulrich R; Koletzki D; Lachmann S; Lundkvist A; Zankl A; Kazaks A; Kurth A; Gelderblom H R; Borisova G; Meisel H; Kruger D H. (Institute of Virology, Humboldt University, Charite Medical School, Berlin, Germany.) Journal of biotechnology, (1999 Aug 20) 73 (2-3) 141-53. Ref: 41. Journal code: 8411927. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.

AB Virus-like particles generated by the heterologous expression of virus structural proteins are able to potentiate the immunogenicity of foreign epitopes presented on their surface. In recent years epitopes of various origin have been inserted into the core antigen of hepatitis B virus (HBV) allowing the formation of chimaeric HBV core particles. Chimaeric core particles carrying the 45 N-terminal amino acids of the Puumala hantavirus nucleocapsid protein induced protective immunity in bank voles, the natural host of this hantavirus. Particles applied in the absence of adjuvant are still immunogenic and partially protective in bank voles. Although a C-terminally truncated core antigen of HBV (HBcAg delta) tolerates the insertion of extended foreign sequences, for the construction of **multivalent vaccines** the limited insertion capacity is still a critical factor. Recently, we have described a new system for generating HBV 'mosaic particles' in an Escherichia coli suppressor strain based on a readthrough mechanism on a stop linker located in front of the insert. Those mosaic particles are built up by both HBcAg delta and the HBcAg delta/Puumala nucleocapsid readthrough protein. The particles formed presented the 114 amino acid (aa) long hantavirus sequence, at least in part, on their surface and induced antibodies against the hantavirus sequence in bank voles. Variants of the stop linker still allowed the formation of mosaic particles demonstrating that stop codon

suppression alone is sufficient for the packaging of longer foreign sequences in mosaic particles. Another approach to increase the insertion capacity is based on the simultaneous insertion of different Puumala nucleocapsid protein sequences (aa 1-45 and aa 75-119) into two different positions (aa 78 and behind aa 144) of a single HBcAg molecule. The data presented are of high relevance for the generation of **multivalent vaccines** requiring a high insertion capacity for foreign sequences.

L46 ANSWER 65 OF 162 MEDLINE on STN
1999416391. PubMed ID: 10486923. Polynucleotide vaccines: potential for inducing immunity in animals. Babiuk L A; Lewis J; Suradhat S; Baca-Estrada M; Foldvari M; Babiuk S. (VIDO (Veterinary Infectious Disease Organization), Saskatoon, Canada.) Journal of biotechnology, (1999 Aug 20) 73 (2-3) 131-40. Ref: 61. Journal code: 8411927. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.

AB Polynucleotide immunization has been described as the Third Revolution in Vaccinology. Early studies suggest the potential benefits of this form of immunization including: long-lived immunity, a broad-spectrum of immune responses (both cell mediated immunity, and humoral responses) and the simultaneous induction of immunity to a variety of pathogens through the use of **multivalent vaccines**. Using a murine model, we studied methods to enhance and direct the immune response to polynucleotide vaccines. We demonstrated the ability to modulate the magnitude and direction of the immune response by co-administration of plasmid encoded cytokines and antigen. Also, we clearly demonstrated that the cellular components (cytosolic, membrane-anchored, or extracellular) to which the expressed antigen is delivered determines the types of immune responses induced. Since induction of immunity at mucosal surfaces (route of entry for many pathogens) is critical to prevent infection, various methods of delivering polynucleotide vaccines to mucosal surfaces have been attempted and are described. Expansion of studies in various species, using natural models, should be extremely helpful in demonstrating the universality of this approach to immunization and more importantly, accurately identify parameters that are critical for the development of protective immunity.

L46 ANSWER 66 OF 162 MEDLINE on STN
1999408868. PubMed ID: 10479174. Cross-reactive antibodies prevent the lethal effects of Staphylococcus aureus superantigens. Bavari S; Ulrich R G; LeClaire R D. (Department of Cell Biology and Biochemistry, USAMRIID, Frederick, MD 21702-5011, USA.. sina.bavari@amedd.army.mil) . Journal of infectious diseases, (1999 Oct) 180 (4) 1365-9. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The exotoxins produced by Staphylococcus aureus, staphylococcal enterotoxins (SE) A-E and toxic shock syndrome toxin (TSST)-1, which are associated with serious diseases, including food poisoning and toxic shock syndrome, are termed superantigens (SAgs). To examine whether common antigenic epitopes were present and whether vaccination with 1 bacterial SAg could protect against challenge with a different SE or TSST-1, mice were vaccinated with SEA, SEB, SEC1, or TSST-1 individually or in combination. Mice injected with a single toxin developed high antibody titers against other SAgs. Marked improvement in survival was observed when immunized mice were challenged with a heterologous toxin. Mice vaccinated with a mixture of toxins were fully protected against 1 or multiple toxin challenges, indicating no interference effects of **multivalent vaccinations**. More importantly, higher titers were found against each SAg with the **multivalent vaccination** than with injection with a single SAg. Thus, immunizations with 1 SAg can induce cross-protective antibodies to heterologous SAgs, and multicomponent vaccination can enhance antibody responses against each bacterial SAg.

L46 ANSWER 67 OF 162 MEDLINE on STN
1999254106. PubMed ID: 10318949. Carbohydrate vaccines in cancer: immunogenicity of a fully synthetic globo H hexasaccharide conjugate in man. Slovin S F; Ragupathi G; Adluri S; Ungers G; Terry K; Kim S; Spassova M; Bornmann W G; Fazzari M; Dantis L; Olkiewicz K; Lloyd K O; Livingston P O; Danishefsky S J; Scher H I. (Division of Genitourinary Oncology,

Department of Medicine, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, 1275 York Avenue, New York, NY 10021, USA.. slovins@mskcc.org) . Proceedings of the National Academy of Sciences of the United States of America, (1999 May 11) 96 (10) 5710-5. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The complex carbohydrate molecule globo H hexasaccharide has been synthesized, conjugated to keyhole limpet hemocyanin, and administered with the immunologic adjuvant QS-21 as a vaccine for patients with prostate cancer who have relapsed after primary therapies such as radiation or surgery. Globo H is one of several candidate antigens present on prostate cancer cells that can serve as targets for immune recognition and treatment strategies. The vaccine, given as five subcutaneous vaccinations over 26 weeks, has been shown to be safe and capable of inducing specific high-titer IgM antibodies against globo H. Its immunogenicity was confirmed in prostate cancer patients with a broad range of stages and tumor burdens. Observations of several patients who had evidence of disease relapse restricted to a rising biochemical marker, prostate-specific antigen (PSA), indicated that a treatment effect could occur within 3 months after completion of the vaccine therapy. This effect was manifested as a decline of the slope of the log of PSA concentration vs. time plot after treatment compared with values before treatment. Five patients continue to have stable PSA slope profiles in the absence of any radiographic evidence of disease for more than 2 years. The concept of using PSA slope profiles in assessing early treatment effects in biological therapies such as vaccines awaits further validation in phase II and III trials. The use of a variety of lesser known candidate glycoprotein and carbohydrate antigens in prostate cancer serves as a focus for the development of a **multivalent vaccine** of the treatment of relapsed prostate cancer in patients with minimal tumor burden.

L46 ANSWER 68 OF 162 MEDLINE on STN

1999185204. PubMed ID: 10066464. Vaccination against enteric pathogens: from science to vaccine trials. Lindberg A A. (Pasteur Merieux Connaught, 1541 Avenue Marcel Merieux, 69280 Marcy l'Etoile, France.. alindberg@fr.pmc-vacc.com) . Current opinion in microbiology, (1998 Feb) 1 (1) 116-24. Ref: 35. Journal code: 9815056. ISSN: 1369-5274. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Recent advances in scientific research and clinical trials have shown promise for vaccine development against enteric pathogens. Identification of new virulence factors, such as the two distinct shigella enterotoxins, has allowed the development of new immunogen or new attenuated strains. Improved knowledge facilitated the development of safer attenuated live microorganism and construction of **multivalent vaccines**. Finally, an important advantage is the use of nonreplicating plasmid DNA vectors to express protective antigens in the host.

L46 ANSWER 69 OF 162 MEDLINE on STN

1999150444. PubMed ID: 10024434. Identification and grouping of Dichelobacter nodosus, using PCR and sequence analysis. John G H; Smith R; Abraham K J; Ellis R P. (Department of Microbiology & Molecular Genetics, Oklahoma State University, Stillwater, OK, USA.) Molecular and cellular probes, (1999 Feb) 13 (1) 61-5. Journal code: 8709751. ISSN: 0890-8508. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Dichelobacter nodosus is the causative agent of ovine foot rot, a disease that is a constant economic burden for many Western sheep ranches. Vaccination is one method of treating foot rot. A higher and more specific immune response is observed when monovalent vaccines are used to treat foot rot, as compared to **multivalent vaccines**, which incorporate all 10 major New Zealand D. nodosus serogroups. There is no single assay for specifically identifying and grouping D. nodosus for the purpose of incorporating only the desired serogroup(s) in a vaccine. A polymerase chain reaction (PCR)-based assay was used to specifically identify and group D. nodosus from a foot rot lesion. Identification and grouping was determined by predicted fragment size analysis and nucleotide sequence information. The PCR approach vastly improves the accuracy in identifying

and grouping B. Nodosus from a ... lesion.

L46 ANSWER 70 OF 162 MEDLINE on STN
1999141627. PubMed ID: 9987154. Multivalent group A streptococcal vaccine designed to optimize the immunogenicity of six tandem M protein fragments. Dale J B. (Veterans Affairs Research Service, University of Tennessee, Memphis 38104, USA. dale.james_b +. @memphis.med.va.gov) . Vaccine, (1999 Jan) 17 (2) 193-200. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB One of the major challenges in the development of group A streptococcal M protein-based vaccines is the multiplicity of M types expressed by these organisms. Previous studies have shown that **multivalent vaccines** containing as many as eight M protein fragments in tandem were immunogenic and evoked opsonic antibodies. It was also noted that the C-terminal fragments of these hybrid proteins were often not immunogenic or evoked only low levels of opsonic antibodies, suggesting that the C-terminus of the molecule may have been preferentially degraded or altered in vivo. In the present studies, we designed a hexavalent vaccine containing protective M protein peptides from types 24, 5, 6, 19, 1, and 3 group A streptococci. In order to "protect" the carboxy-terminal components, the amino-terminal M24 fragment was reiterated on the carboxy-terminal end of the construct. The hexavalent vaccine was immunogenic in laboratory animals and evoked high titers of antibodies against each of the native M proteins represented in the vaccine and bactericidal antibodies against all six sterotypes of group A streptococci. The vaccine was equally immunogenic when delivered in alum or in complete Freund's adjuvant. None of the immune sera contained antibodies that crossreacted with human heart tissue. Our results show that complex multivalent group A streptococcal vaccines can be designed in such a way that each M protein fragment is immunogenic and evokes protective antibodies.

L46 ANSWER 71 OF 162 MEDLINE on STN
1999140741. PubMed ID: 9988242. Clinical and economic impact of a combination Haemophilus influenzae and Hepatitis B vaccine: estimating cost-effectiveness using decision analysis. Fendrick A M; Lee J H; LaBarge C; Glick H A. (Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor, USA.. amfen@umich.edu) . Archives of pediatrics & adolescent medicine, (1999 Feb) 153 (2) 126-36. Journal code: 9422751. ISSN: 1072-4710. Pub. country: United States. Language: English.

AB BACKGROUND: Compliance with hepatitis B virus (HBV) vaccine remains suboptimal, despite a recommendation by the Advisory Committee on Immunization Practices of the US Public Health Service that all newborns be vaccinated. Although a combined HBV-Haemophilus influenzae type b (Hib) vaccine may improve acceptance of the HBV vaccine, the clinical and economic consequences of this intervention are uncertain. OBJECTIVES: To compare the health impact and cost-effectiveness of the following 2 immunization strategies: current practice of administering HBV vaccine separately (75% compliance) and Hib vaccine alone or as part of a **multivalent vaccine** (95% compliance); and strategy of delivering a combined HBV-Hib vaccine (95% compliance). DESIGN: A Markov model simulated the natural history of acute and chronic HBV and Hib disease in a cohort of US newborns. Clinical and economic variables were obtained from published reports. RESULTS: The Hib-related outcomes were the same in both strategies, because the efficacy and compliance with Hib vaccine were assumed to be equivalent in both. A 53% reduction in the number of cases of HBV infection with the combination strategy (n = 8541) was estimated when compared with current practice (n = 18 044), along with 205 fewer HBV-related deaths per 1 million infants. Immunization costs of the combination strategy were $11.5 million higher than for current practice ($108.4 million compared with $96.9 million), whereas the cost of HBV-related disease was $4.0 million lower than in current practice. The incremental cost-effectiveness ratio for the combination strategy was $17700 per year of life saved. CONCLUSION: An HBV-Hib vaccine in US infants yields substantial benefits, with a cost-effectiveness ratio that

is lower than that of many commonly used medical interventions.

L46 ANSWER 72 OF 162 MEDLINE on STN
1999106729. PubMed ID: 9890055. Weighing the risks and benefits of vaccination. Glickman L T. (Department of Veterinary Pathobiology, Purdue University, West Lafayette, Indiana 47907, USA.) Advances in veterinary medicine, (1999) 41 701-13. Ref: 24. Journal code: 9714525. ISSN: 1093-975X. Pub. country: United States. Language: English.

AB The following summarizes this author's current thoughts regarding veterinary vaccines and their safety: 1. Every licensed animal vaccine is probably effective, but also produces some adverse effects. 2. Prelicensing studies of vaccines are not specifically designed to detect adverse vaccine reactions. 3. An improved system of national postmarketing surveillance is required to identify most adverse vaccine reactions that occur at low and moderate frequency. 4. Even a good postmarketing surveillance system is unlikely, however, to detect delayed adverse vaccine reactions, and the longer the delay the less likely they will be associated with vaccination. 5. Analytic epidemiologic (field) studies are the best way to link vaccination with delayed adverse reactions, but these are often hindered by incomplete vaccination histories in medical records in veterinary practice and by a lack of veterinarians in industry trained in epidemiologic methods. 6. Each licensed veterinary vaccine should be subjected to a quantitative risk assessment, and these should be updated on a regular basis as new information becomes available. 7. Risk assessment should be used to identify gaps in information regarding the safety and efficacy of vaccines, and appropriate epidemiologic studies conducted to fill these gaps that contribute to the uncertainty in risk estimates. 8. Risk assessment is an analytical process that is firmly based on scientific considerations, but it also requires judgments to be made when the available information is incomplete. These judgments inevitably draw on both scientific and policy considerations. 9. Representatives from industry, government, veterinary medicine, and the animal-owning public should be involved in risk management, that is, deciding between policy options. The controversy regarding vaccine risks is intensifying to the point that some animal owners have stopped vaccinating their animals. They offer as justification the belief that current vaccines are "just too dangerous." Some owners report that since they completely stopped vaccinating their animals, they have been healthy. What they fail to realize is that a high percentage of animal owners are responsible and do vaccinate their animals, thus providing "herd immunity" protection to the unvaccinated animals whom they contact. The solution to the vaccine controversy is not to abandon vaccination as an effective means of disease prevention and control, but rather to encourage vaccine research to answer important questions regarding safety and to identify the biological basis for adverse reactions. Key questions to be answered include these: What components of vaccines are responsible for adverse reactions? What is the genetic basis for susceptibility to adverse health effects in animals? How can susceptible individuals be identified? Do **multivalent vaccines** cause a higher rate of adverse reactions than monovalent vaccines? Is administration of multiple doses of monovalent vaccines really any safer than administering a single **multivalent vaccine**? These and other vaccine-related questions deserve our attention as veterinarians so we can fulfill our veterinary oath to relieve animal suffering and "above all else, do no harm."

L46 ANSWER 73 OF 162 MEDLINE on STN
1999102578. PubMed ID: 9847325. Chimeric lyssavirus glycoproteins with increased immunological potential. Jallet C; Jacob Y; Bahloul C; Drings A; Desmezieres E; Tordo N; Perrin P. (Laboratoire des Lyssavirus, Institut Pasteur, 75724 Paris Cedex 15, France.) Journal of virology, (1999 Jan) 73 (1) 225-33. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The rabies virus glycoprotein molecule (G) can be divided into two parts separated by a flexible hinge: the NH2 half (site II part) containing antigenic site II up to the linear region (amino acids [aa] 253 to 275

containing antigenic site III and the transmembrane and cytoplasmic domains. The structural and immunological roles of each part were investigated by cell transfection and mouse DNA-based immunization with homogeneous and chimeric G genes formed by fusion of the site II part of one genotype (GT) with the site III part of the same or another GT. Various site II-site III combinations between G genes of PV (Pasteur virus strain) rabies (GT1), Mokola (GT3), and EBL1 (European bat lyssavirus 1 [GT5]) viruses were tested. Plasmids pGPV-PV, pGMok-Mok, pGMok-PV, and pGEBL1-PV induced transient expression of correctly transported and folded antigens in neuroblastoma cells and virus-neutralizing antibodies against parental viruses in mice, whereas, pG-PVIII (site III part only) and pGPV-Mok did not. The site III part of PV (GT1) was a strong inducer of T helper cells and was very effective at presenting the site II part of various GTs. Both parts are required for correct folding and transport of chimeric G proteins which have a strong potential value for immunological studies and development of **multivalent vaccines**. Chimeric plasmid pGEBL1-PV broadens the spectrum of protection against European lyssavirus genotypes (GT1, GT5, and GT6).

L46 ANSWER 74 OF 162 MEDLINE on STN
1999094619. PubMed ID: 9880010. Compatibility of plasmids expressing different antigens in a single DNA vaccine formulation. Braun R; Babiuk L A; van Drunen Littel-van den Hurk. (Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Canada.) Journal of general virology, (1998 Dec) 79 (Pt 12) 2965-70. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB One anticipated advantage of DNA immunization is the potential to create **multivalent vaccines**. We have examined the effects of mixing plasmids into single formulations using plasmids expressing four different membrane bound glycoproteins from bovine herpesvirus-1 (BHV-1), bovine parainfluenzavirus-3 (bPI3) and human influenza virus (HINF). Plasmids were delivered by intradermal injection into the tails of mice and the types of responses generated were clearly affected by the expressed antigen. Plasmids expressing glycoproteins B and D of BHV-1, and the haemagglutinin/ neuraminidase of bPI3, generated responses with a predominance of IgG1, suggestive of a Th2 type of response. In contrast, the plasmid expressing HINF haemagglutinin induced an antibody response biased towards IgG2a, indicating a Th1 type of response. In most instances the mixing of plasmids had only slight effects on the magnitude or bias of the responses to the individual components. However, under certain conditions we found that addition of a second plasmid converted an IgG2a biased response to a response with primarily IgG1 antibody. The reverse situation (i.e. an IgG1 conversion to IgG2a), however, was not found. These findings have important implications for the development of **multivalent vaccines**.

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L46 ANSWER 25 OF 162 MEDLINE on STN
2002583246. PubMed ID: 12348372. The Children's Vaccine Initiative. Caddell A. Africa health, (1997 Nov) 20 (1) 15. Journal code: 7905114. ISSN: 0141-9536.
Report No.: PIP-130971; POP-00277437. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The Children's Vaccine Initiative (CVI), which was founded after the World Summit for Children held in New York in September 1990, had three goals: 1) immunization of all children; 2) research to determine the feasibility of a single-dose **multivalent vaccine**; and 3) introduction of new vaccines for infectious diseases. UNICEF, UNDP, WHO, the World Bank, and the Rockefeller Foundation co-sponsored the CVI. The following has been achieved since 1990: 1) coverage with 6 EPI vaccines has risen above 80% in many countries; 2) the number of vaccines in the research pipeline has increased; 3) there is better planning of the global vaccine supply; and 4) governments of developing countries are assuming more responsibility

for national immunization. The new strategic plan for CVI, which is the work of experts from government, industry, and international organization, establishes the following goals: 1) development of greater consensus on priorities regarding vaccine development and application; 2) definition of needs and strategies for action; 3) communication of the health and economic value of vaccines; and 4) mobilization of resources. Executive Secretary Dr. Lee and CVI coordinator Roy Widdus are responsible for the new role for CVI. 4 million children die annually from diseases preventable by existing vaccines; another 8 million die annually from diseases that could be prevented by new vaccines. Measles, hepatitis B, and Hib vaccines are underused. Vaccines against rotavirus diarrhea and pneumococcal pneumonia should be available soon, while research continues on vaccines against malaria and HIV.

L46 ANSWER 26 OF 162 MEDLINE on STN
2002427986. PubMed ID: 12184701. Evaluation of antithyroglobulin antibodies after routine vaccination in pet and research dogs. Scott-Moncrieff J Catharine; Azcona-Olivera Juan; Glickman Nita W; Glickman Lawrence T; HogenEsch Harm. (Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN 47907, USA.) Journal of the American Veterinary Medical Association, (2002 Aug 15) 221 (4) 515-21. Journal code: 7503067. ISSN: 0003-1488. Pub. country: United States. Language: English.

AB OBJECTIVE: To determine whether routine vaccination induces antibodies against bovine thyroglobulin and autoantibodies against canine thyroglobulin in dogs. DESIGN: Prospective study. ANIMALS: 20 healthy research Beagles and 16 healthy pet dogs. PROCEDURE: For the research Beagles, 5 dogs were vaccinated with a **multivalent vaccine** and a rabies vaccine, 5 dogs received only the **multivalent vaccine**, 5 dogs received only the rabies vaccine, and 5 dogs were unvaccinated controls. The **multivalent vaccine** was administered at 8, 10, 12, 16, 20, 26, and 52 weeks of age and every 6 months thereafter. The rabies vaccine was administered at 16 and 52 weeks of age and then once per year. Blood was collected from all dogs at 8, 16, and 26 weeks of age and then 4 times yearly. Assays for antibodies directed against bovine and canine thyroglobulin were performed prior to and 2 weeks after each yearly vaccination. For the pet dogs, blood was collected prior to and 2 weeks after 1 vaccination. RESULTS: In the research Beagles, there was a significant increase in anti-bovine thyroglobulin antibodies in all vaccinated dogs, compared with control dogs. There was a significant increase in anti-canine thyroglobulin antibodies in the 2 groups of dogs that received the rabies vaccine but not in the group that received the **multivalent vaccine** alone. In the pet dogs, there was a significant increase in anti-canine thyroglobulin antibodies after vaccination but no significant change in anti-bovine thyroglobulin antibodies. CONCLUSIONS AND CLINICAL RELEVANCE: Recent vaccination may result in increased anti-canine thyroglobulin antibodies. Whether these antibodies have a deleterious effect on canine thyroid function is unknown.

L46 ANSWER 27 OF 162 MEDLINE on STN
2002422973. PubMed ID: 12180882. Derivation, safety and efficacy of a Marek's disease vaccine developed from an Australian isolate of very virulent Marek's disease virus. Karpathy R C; Firth G A; Tannock G A. (Intervet (Australia) Pty Ltd, Vaccine Production Laboratory, Beresfield, New South Wales.) Australian veterinary journal, (2002 Jan-Feb) 80 (1-2) 61-6. Journal code: 0370616. ISSN: 0005-0423. Pub. country: Australia. Language: English.

AB OBJECTIVE: To develop a serotype 1 Marek's disease (MD) vaccine from a very virulent MDV (vvMDV) pathotype and demonstrate safety and efficacy against early challenge with very virulent field strains in the presence of maternal antibody. STUDY DESIGN: Strain BH 16 was isolated and attenuated by serial cell culture passage. One of two cloned passages was selected for vaccine development following early laboratory-scale protection trials in commercial birds. Comparative protection trials were carded out on the BH 16 vaccine and on a CVI 988 Rispens vaccine using commercial and SPF chickens. Challenge viruses used were either a low

passage strain BH 16 virus, the Woodlands No. 1 strain or HPRS strain of MDV. The BH 16 vaccine was back-passaged in SPF chickens six times and virus recovered from the final passage and the original vaccine virus were tested for safety. The immunosuppressive potential of the BH 16 and Rispens vaccines was also assessed in parallel. RESULTS: The BH 16 and Rispens vaccines induced comparable levels of protection when used as monovalent or **multivalent vaccines**, although protection achieved with the monovalent vaccines was lower. No gross tumour formation was evident in any birds receiving the BH 16 vaccine or bird-passaged virus, although microscopic lesions were present in 2/12 birds that received the bird-passaged virus. In tests for immunosuppression, there was no histological evidence of damage to either the bursa of Fabricius or the thymus. CONCLUSION: The BH 16 vaccine was shown to be safe and at least as protective as the Rispens vaccine against three highly virulent MD challenge viruses.

L46 ANSWER 28 OF 162 MEDLINE on STN
2002276314. PubMed ID: 12006514. Induction of p53-specific immune responses in colorectal cancer patients receiving a recombinant ALVAC-p53 candidate vaccine. van der Burg Sjoerd H; Menon Anand G; Redeker Anke; Bonnet Marie-Claude; Drijfhout Jan Wouter; Tollenaar Rob A E M; van de Velde Cornelis J H; Moingeon Philippe; Kuppen Peter J K; Offringa Rienk; Melief Cornelis J M. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, 2300 RC Leiden, the Netherlands.. shvdburg@worldonline.nl) . Clinical cancer research : an official journal of the American Association for Cancer Research, (2002 May) 8 (5) 1019-27. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB PURPOSE: The tumor-associated auto-antigen p53 is commonly overexpressed in various types of human cancer, including colorectal cancer. Experiments in preclinical models have shown that it can serve as a target for T-cell-mediated tumor-eradication. The feasibility of a p53-specific therapeutic vaccination was investigated in cancer patients. EXPERIMENTAL DESIGN: A Phase I/II dose-escalation study was performed that evaluated the effect of a recombinant canarypoxvirus (ALVAC) vaccine encoding wild-type human p53 in 15 patients with advanced colorectal cancer. Each group of five patients received three i.v. doses of one-tenth of a dose, one-third of a dose, or 1 dose of the vaccine [1 dose = 1 x 10(7.5) cell culture infectious dosis (CCID)50]. RESULTS: Potent T-cell and IgG antibody responses against the vector component of the ALVAC vaccine were induced in the majority of the patients. Enzyme-linked immunosorbent-spot assay (ELISPOT) analysis of vaccine-induced immunity revealed the presence of IFN-gamma-secreting T cells against both ALVAC and p53, whereas no significant interleukin-4 responses were detected. Vaccine-mediated enhancement of p53-specific T-cell immunity was found in two patients in the highest-vaccine-dose group. CONCLUSIONS: This study demonstrated the feasibility, even in patients with advanced cancer, to elicit immune responses against the ubiquitously expressed tumor-associated auto-antigen p53. Our results form the basis for additional studies that will explore the antitumor capacity of p53 containing **multivalent vaccines** in cancer patients with limited tumor burden.

L46 ANSWER 29 OF 162 MEDLINE on STN
2002205671. PubMed ID: 11939328. Effect of vaccination on serum concentrations of total and antigen-specific immunoglobulin E in dogs. HogenEsch Harm; Dunham Anisa D; Scott-Moncrieff Catharine; Glickman Larry T; DeBoer Douglas J. (Department of Veterinary Pathobiology, Purdue University, West Lafayette, IN 47907, USA.) American journal of veterinary research, (2002 Apr) 63 (4) 611-6. Journal code: 0375011. ISSN: 0002-9645. Pub. country: United States. Language: English.

AB OBJECTIVE: To determine the effect of vaccination on serum concentrations of total and antigen-specific IgE in dogs. ANIMALS: 20 female Beagles. PROCEDURE: Groups of 5 dogs each were vaccinated repeatedly between 8 weeks and 4 years of age with a multivalent and rabies vaccine, a **multivalent vaccine** only, or a rabies vaccine only. A fourth group of 5 dogs served as unvaccinated controls. Serum concentrations of total

immunoglobulins and antigen-specific IgE were determined following vaccination. RESULTS:-The **multivalent vaccine** had little effect on serum total IgE concentrations. The concentration of IgE increased slightly following vaccination for rabies at 16 weeks and 1 year of age and increased greatly after vaccination at 2 and 3 years of age in most dogs, with a distinct variation between individual dogs. Vaccination had no effect on serum concentrations of IgA, IgG, and IgM as measured at 2 and 3 years of age. The rabies vaccine contained aluminum adjuvant in contrast to the **multivalent vaccine**. An increase of IgE that was reactive with vaccine antigens, including bovine serum albumin and bovine fibronectin, was detected in some of the dogs vaccinated for rabies. There was no significant correlation between serum concentrations of total IgE and antigen-specific IgE following vaccination. Serum total IgE concentration rapidly returned to preimmunization concentrations in most dogs, but high concentrations of antigen-specific IgE persisted. CONCLUSIONS AND CLINICAL RELEVANCE: Vaccination of dogs for rabies increases serum concentrations of total IgE and induces IgE specific for vaccine antigens, including tissue culture residues. Vaccination history should be considered in the interpretation of serum total IgE concentrations.

L46 ANSWER 30 OF 162 MEDLINE on STN
2002188639. PubMed ID: 11895984. Immunogenicity of a 26-valent group A streptococcal vaccine. Hu Mary C; Walls Michael A; Stroop Steven D; Reddish Mark A; Beall Bernard; Dale James B. (ID Biomedical Corporation, Bothell, Washington, USA.) Infection and immunity, (2002 Apr) 70 (4) 2171-7. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB A **multivalent vaccine** containing amino-terminal M protein fragments from 26 different serotypes of group A streptococci was constructed by recombinant techniques. The vaccine consisted of four different recombinant proteins that were formulated with alum to contain 400 microg of protein per dose. Rabbits were immunized via the intramuscular route at 0, 4, and 16 weeks. Immune sera were assayed for the presence of type-specific antibodies against the individual recombinant M peptides by enzyme-linked immunosorbent assay and for opsonic antibodies by in vitro opsonization tests and indirect bactericidal tests. The 26-valent vaccine was highly immunogenic and elicited fourfold or greater increases in antibody levels against 25 of the 26 serotypes represented in the vaccine. The immune sera were broadly opsonic and were bactericidal against the majority of the 26 different serotypes. Importantly, none of the immune sera cross-reacted with human tissues. Our results indicate that type-specific, protective M protein epitopes can be incorporated into complex, **multivalent vaccines** designed to elicit broadly protective opsonic antibodies in the absence of tissue-cross-reactive antibodies.

L46 ANSWER 31 OF 162 MEDLINE on STN
2002141275. PubMed ID: 11860550. Stability and activity of specific antibodies against Streptococcus mutans and Streptococcus sobrinus in bovine milk fermented with Lactobacillus rhamnosus strain GG or treated at ultra-high temperature. Wei H; Loimaranta V; Tenovuo Jorma; Rokka S; Syvaoja E-L; Korhonen H; Joutsjoki V; Marnila P. (Agrifood Research Finland, Food Research, Jokioinen, Finland.) Oral microbiology and immunology, (2002 Feb) 17 (1) 9-15. Journal code: 8707451. ISSN: 0902-0055. Pub. country: Denmark. Language: English.

AB Passive local immunization against dental caries is a promising approach to its prevention, as clinical evidence of active oral or nasal immunization is still limited and controversial. By means of systemic immunization of pregnant cows with a **multivalent vaccine**, high titres of IgG antibodies against human cariogenic bacteria, Streptococcus mutans and Streptococcus sobrinus, were produced in bovine colostrum. The purified immune product (IP) of this preparation has a number of anticariogenic properties, such as inhibition of streptococcal adherence to saliva-coated hydroxyapatite and inhibition of glucosyltransferase enzymes. This study investigated whether IP antibodies remained active and functional when added to ultra-high temperature (UHT)-treated milk or

of Lactobacillus rhamnosus GG (LGG) fermented milk stored for an extended time. LGG was chosen because of its widely known health benefits in humans and animals. A commercial UHT toddler's milk was supplemented with IP and stored for 2 months at 5, 21 and 30 degrees C. The antistreptococcal titres in UHT milk did not decline at any temperature during storage, and UHT-IP inhibited the adherence of S. mutans for up to 2 months. This was not the case with UHT toddler's milk without IgG antibodies. Milk was fermented with live LGG cells in the presence or absence of 5% IP. The antistreptococcal titres declined to about 30% of the original titres after storage. Fresh milk alone slightly enhanced streptococcal adhesion but fresh milk with IP inhibited the adherence of S. mutans by over 50%. LGG-positive fermented milk without antibodies also inhibited (P < 0.05) the adhesion by about 40%. In both LGG-fermented and UHT immune milk, the activity of antibodies against cariogenic streptococci was maintained during the expected shelf-life of these products. From the anticariogenic point of view it may be beneficial to add bovine-specific antibodies against mutans streptococci to probiotic LGG-containing milk products.

L46 ANSWER 32 OF 162 MEDLINE on STN
2002128112. PubMed ID: 11863272. The pneumococcus: carriage, disease and conjugate vaccines. Obaro Steven; Adegbola Richard. (Department of Paediatrics, Imperial College School of Medicine, St Mary's Hospital, London UK.. sobaro@ic.ac.uk) . Journal of medical microbiology, (2002 Feb) 51 (2) 98-104. Ref: 50. Journal code: 0224131. ISSN: 0022-2615. Pub. country: England: United Kingdom. Language: English.

AB Modern biotechnology has made possible the rapid development and introduction into clinical care of a wide spectrum of potent antimicrobial agents. However, the battle against Streptococcus pneumoniae (pneumococcus) has remained fierce, as acquisition of resistance is even more rapid and these antimicrobial agents are rendered ineffective. Obtaining appropriate antibiotic treatment for severe invasive pneumococcal infections is now a major challenge in many regions of the world. The ground-breaking success of Haemophilus influenzae type b (Hib) conjugate vaccine has brought hope for the conquest of other capsulate bacteria. Recent results of efficacy trials of a heptavalent pneumococcal conjugate vaccine bring hope that protein conjugate vaccines will have a similar impact on pneumococcal disease. These **multivalent vaccine** formulations include pneumococcal serotypes that most often acquire antibiotic resistance and there is hope that the widespread application of these vaccines will decrease the incidence of multi-drug-resistant infections. The potential reduction of pneumococcal disease could even extend to unimmunised younger siblings and the elderly residing with immunised young children, through its herd effect. However, in view of the multiplicity of serotypes and the biology of the pneumococcus, optimism must be tempered by caution.

L46 ANSWER 33 OF 162 MEDLINE on STN
2002101971. PubMed ID: 11833821. Development of hypertrophic osteodystrophy and antibody response in a litter of vaccinated Weimaraner puppies. Harrus S; Waner T; Aizenberg; Safra N; Mosenco A; Radoshitsky M; Bark H. (Department of Clinical Sciences, School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel.) Journal of small animal practice, (2002 Jan) 43 (1) 27-31. Journal code: 0165053. ISSN: 0022-4510. Pub. country: England: United Kingdom. Language: English.

AB Two different vaccination protocols were compared with regard to the development of hypertrophic osteodystrophy (HOD) (also termed metaphyseal osteopathy) and effectiveness of immunisation in a litter of 10 Weimaraner puppies. Five puppies (group 1) were vaccinated with a modified live canine parvovirus vaccine (CPV) and then two weeks later with a trivalent vaccine containing modified live canine distemper virus and adenovirus type 2 combined with a Leptospira bacterin (DHL). The CPV and DHL vaccine protocols were administered a further two times, at two-week intervals. Group 2 was vaccinated with three consecutive **multivalent vaccines** containing modified live canine distemper virus, canine parvovirus, parainfluenza and adenovirus type 2 combined with a Leptospira bacterin,

eight weeks. Three dogs in group 1 developed HOD, while all five dogs in group 2 developed HOD during the study period. Dogs in group 2 had more episodes of HOD than those in group 1. Dogs in group 1 developed higher antibody titres to canine distemper virus and parvovirus compared with those in group 2. Only two out of the 10 dogs developed protective antibody titres to parvovirus. The results of this study suggest that the two different vaccination protocols affected the pattern of appearance of HOD and immunisation in this litter of Weimaraner puppies. The results obtained and the previously reported data suggest that a larger controlled study is needed to further elucidate the effect of different vaccination protocols on HOD and immunisation in Weimaraner puppies.

L46 ANSWER 34 OF 162 MEDLINE on STN
2002077000. PubMed ID: 11803081. A simple selection system for construction of recombinant gD-negative pseudorabies virus as a vaccine vector. Shiau Ai Li; Liu Chia Wen; Wang Shiang Yiu; Tsai Chiau Yuang; Wu Chao Liang. (Department of Microbiology, National Cheng Kung University Medical College, 1 Dashiue Road, 701, Tainan, Taiwan.) Vaccine, (2002 Jan 15) 20 (7-8) 1186-95. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB We describe a simple, efficient two-step method for construction of glycoprotein D (gD)-negative pseudorabies virus (PrV) carrying transgenes inserted in place of the gD gene. The first step was the use of the thymidine kinase (TK) gene of herpes simplex virus (HSV) for insertional inactivation of the gD gene in a PrV mutant deficient in both TK and glycoprotein E (gE). The gD-negative, HSV-TK-positive mutant could be selected in HAT medium. The second step was substitution of HSV-TK with other genes of interest. The resultant gD/gE/TK-negative mutant was easily isolated by acyclovir selection. The expression of the transgene was detectable in vivo and the antibody responses against both inserted antigens and PrV were induced. The protective efficacy of the gD/gE/TK-negative PrV against lethal PrV challenge was also demonstrated. This PrV mutant carrying immunogenic proteins from unrelated porcine pathogens may be tested as a **multivalent vaccine** candidate for swine.

L46 ANSWER 35 OF 162 MEDLINE on STN
2002037511. PubMed ID: 11764325. Effect of selenium and vitamin E on antibody production by dairy cows vaccinated against Escherichia coli. Panousis N; Roubies N; Karatzias H; Frydas S; Papasteriadis A. (Clinic of Productive Animal Medicine, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, Greece.) Veterinary record, (2001 Nov 24) 149 (21) 643-6. Journal code: 0031164. ISSN: 0042-4900. Pub. country: England: United Kingdom. Language: English.

AB Sixty clinically healthy Holstein cows were randomly assigned to one of four groups according to their age and parity and vaccinated in late pregnancy (day 190) with a **multivalent vaccine** against Escherichia coli. The 15 cows in the first group (SeE) were injected intramuscularly with a solution of sodium selenite (0.1 mg Se/kg bodyweight) and vitamin E (alpha-tocopherol acetate, 8 U/kg bodyweight), the cows in the second group (Se) received only selenium and the cows in the third group (E) received only vitamin E at the same doses and by the same route of administration; the cows in the fourth group were used as controls. The vaccination and the injections of selenium and vitamin E were repeated 42 days later. The concentration of selenium in whole blood and of vitamin E in serum was determined by fluorometric methods. Specific antibody titres against E coli were determined in serum samples by ELISA. The results showed that the injection of selenium either alone or in combination with vitamin E significantly improved the production of specific antibodies against E coli, and that the production of specific antibodies was greater after the administration of selenium alone.

L46 ANSWER 36 OF 162 MEDLINE on STN
2002017257. PubMed ID: 11432433. Antibody testing against canine coronavirus by immunoperoxidase plaque staining. Soma T; Hara M; Ishii H; Yamamoto S. (Veterinary Diagnostic Laboratory, Marupi Lifetech Co, Ltd,

(4) 327-36. Journal code: 8100520. ISSN: 0165-7380. Pub. country: Netherlands. Language: English.

AB The application of the immunoperoxidase (IP) plaque staining procedure (IP test) to the diagnosis of canine coronavirus (CCV) infection was investigated. The IP test did not react with sera from either 15 specific pathogen-free (SPF) dogs or 7 SPF dogs immunized with a **multivalent vaccine**, including canine parvovirus type 2, canine distemper virus, canine adenovirus type 2, and canine parainfluenza virus. To compare the IP test with the neutralizing test (NT), sera from 240 healthy dogs and from 3 experimentally CCV-infected dogs were examined. All 60 sera positive for NT antibody were positive for IP antibody, and all 180 sera negative for NT antibody were negative for IP antibody in the healthy dogs. The IP titres showed similar changes with time after CCV inoculation to those of the NT titres in the experimentally infected dogs. These findings indicate that the IP test specifically detected anti-CCV antibodies. When the IP test and NT were compared in dogs with diarrhoeic signs. 2.1% of 48 sera and 20.3% of 74 sera, which were all negative for NT antibody, were positive for IP antibody in the dogs of under one year of age and at least one year of age, respectively. The difference between the IP and NT titres (log10 [reciprocal of IP titre] log10 [reciprocal of NT titre]) for the diarrhoeic dogs of under one year of age (2.350 +/- 0.931) was significantly larger than that for the healthy dogs (0.982 +/- 0.447) (p<0.0001), the NT titre being negative or very low, despite a high IP titre in many diarrhoeic dogs. Hence, the IP test is more able to detect anti-CCV antibodies, especially in dogs showing clinical signs. The IP-positivity rate was significantly higher in the diarrhoeic dogs of under one year of age (48.7%) than in the healthy dogs (25.0%) (chi2 = 19.844, p<0.0001), suggesting that CCV may contribute to diarrhoea in many juvenile dogs.

L46 ANSWER 37 OF 162 MEDLINE on STN
2001668242. PubMed ID: 11713814. DNA-based immunisation against rabies and rabies-related viruses: towards **multivalent vaccines**. Perrin P; Jacob Y; Desmezieres E; Tordo N. (Lyssavirus Laboratory, Institut Pasteur, Paris, France.) Developments in biologicals, (2000) 104 151-7. Journal code: 100940058. ISSN: 1424-6074. Pub. country: Switzerland. Language: English.

AB Prototypes of multivalent DNA vaccines against lyssaviruses (LV: rabies and rabies-related viruses) and other viruses were developed using chimaeric LV glycoprotein (cLVG) DNA and cLVG DNA carrying foreign epitopes. cLVG is composed of the N-terminal half of an LV genotype (GT) containing antigenic site II, the C-terminal half of GT containing antigenic site III, as well as the transmembrane and cytoplasmic domains of the same or a different GT. Both antigenic sites induced virus neutralizing antibodies (VNAb). Foreign B and T cell epitopes inserted between the two halves of cLVG correspond to the B cell C3 neutralisation epitope of poliovirus VP1 protein and to the H2d CMH I restricted T cell epitope of the nucleoprotein of the lymphocytic choriomeningitis virus (LCMV). In mice and dogs homogenous rabies virus G DNA induced protection against wild-type rabies virus whereas cLVG protected against lyssaviruses. cLVG DNA carrying foreign epitopes induced VNAb against LV and poliovirus and protection against LCMV. The results obtained clearly demonstrate the potential usefulness of cLVG for the development of **multivalent vaccines** against viral diseases, including rabies and zoonoses.

L46 ANSWER 38 OF 162 MEDLINE on STN
2001639983. PubMed ID: 11689649. Individual and bivalent vaccines based on alphavirus replicons protect guinea pigs against infection with Lassa and Ebola viruses. Pushko P; Geisbert J; Parker M; Jahrling P; Smith J. (Virology Division, United States Army Medical Research Institute for Infectious Diseases, Fort Detrick, Frederick, Maryland 21702, USA.. peter.pushko@amedd.army.mil) . Journal of virology, (2001 Dec) 75 (23) 11677-85. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Lassa and Ebola viruses cause acute, often fatal, hemorrhagic fever diseases, for which no effective vaccines are currently available. Although lethal human disease outbreaks have been confined so far to sub-Saharan Africa, they also pose significant epidemiological concern worldwide as demonstrated by several instances of accidental importation of the viruses into North America and Europe. In the present study, we developed experimental individual vaccines for Lassa virus and bivalent vaccines for Lassa and Ebola viruses that are based on an RNA replicon vector derived from an attenuated strain of Venezuelan equine encephalitis virus. The Lassa and Ebola virus genes were expressed from recombinant replicon RNAs that also encoded the replicase function and were capable of efficient intracellular self-amplification. For vaccinations, the recombinant replicons were incorporated into virus-like replicon particles. Guinea pigs vaccinated with particles expressing Lassa virus nucleoprotein or glycoprotein genes were protected from lethal challenge with Lassa virus. Vaccination with particles expressing Ebola virus glycoprotein gene also protected the animals from lethal challenge with Ebola virus. In order to evaluate a single vaccine protecting against both Lassa and Ebola viruses, we developed dual-expression particles that expressed glycoprotein genes of both Ebola and Lassa viruses. Vaccination of guinea pigs with either dual-expression particles or with a mixture of particles expressing Ebola and Lassa virus glycoprotein genes protected the animals against challenges with Ebola and Lassa viruses. The results showed that immune responses can be induced against multiple vaccine antigens coexpressed from an alphavirus replicon and suggested the possibility of engineering **multivalent vaccines** based upon alphavirus vectors for arenaviruses, filoviruses, and possibly other emerging pathogens.

L46 ANSWER 39 OF 162 MEDLINE on STN

2001489509. PubMed ID: 11532129. Identification and characterization of App: an immunogenic autotransporter protein of Neisseria meningitidis. Hadi H A; Wooldridge K G; Robinson K; Ala'Aldeen D A. (Molecular Bacteriology and Immunology Group, Division of Microbiology, School of Clinical Laboratory Sciences, University of Nottingham, Nottingham NG7 2UH, UK.) Molecular microbiology, (2001 Aug) 41 (3) 611-23. Journal code: 8712028. ISSN: 0950-382X. Pub. country: England: United Kingdom. Language: English.

AB In a search for immunogenic virulence factors in Neisseria meningitidis, we have identified a gene encoding a predicted 160 kDa protein with homology to the autotransporter family of proteins. Members of this family are secreted or surface exposed and are often associated with virulence in Gram-negative bacterial pathogens. We named the gene adhesion and penetration protein (app), because of its extensive homology to the hap gene of Haemophilus influenzae. We reconstructed the gene with reference to genomic sequence data and cloned and expressed the protein in Escherichia coli. Rabbit antiserum raised against recombinant App reacted with proteins in all meningococcal isolates examined, which represented clonal groups responsible for the majority of meningococcal invasive disease. Antibodies to the protein were detected in the sera of patients convalescing from meningococcal infection. Purified App had strong stimulating activity for T cells isolated from a number of healthy donors and from one convalescent patient. We confirmed that App is surface localized, cleaved and secreted by N. meningitidis. Importantly, the rabbit anti-App serum killed the organism in the presence of complement. Thus, App is conserved among meningococci, immunogenic in humans and potentially involved in virulence. It therefore merits further investigation as a component of a future **multivalent vaccine**.

L46 ANSWER 40 OF 162 MEDLINE on STN

2001479575. PubMed ID: 11522401. c-DNA vaccination against parasitic infections: advantages and disadvantages. Kofta W; Wedrychowicz H. (Department of Parasitology, Warsaw Agricultural University, Ciszewskiego 8, 02-786, Warsaw, Poland.) Veterinary parasitology, (2001 Sep 12) 100 (1-2) 3-12. Ref: 53. Journal code: 7602745. ISSN: 0304-4017. Pub. country: Netherlands. Language: English.

good prospect for the development of a **multivalent vaccines** that will effectively activate both the humoral and cell mediated mechanisms of the immune system. Currently, DNA vaccination against such important parasitic diseases like malaria, leishmaniosis, toxoplasmosis, cryptosporidiosis, schistosomosis, fasciolosis offers several new opportunities. However, the outcome of vaccination depends very much on vaccine formulations, dose and route of vaccine delivery, and the species and even strain of the vaccinated host. To overcome these problems much research is still needed, specifically focused on cloning and testing of new c-DNA sequences in the following: genome projects: different ways of delivery: design of vectors containing appropriate immunostimulatory sequences and very detailed studies on safety.

L46 ANSWER 41 OF 162 MEDLINE on STN
2001467812. PubMed ID: 11513269. Suspected post-vaccinal acute polyradiculoneuritis in a puppy. Gehring R; Eggars B. (Department of Pharmacology and Toxicology, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa.) Journal of the South African Veterinary Association, (2001 Jun) 72 (2) 96. Journal code: 7503122. ISSN: 1019-9128. Pub. country: South Africa. Language: English.

AB A 4-month-old German shepherd puppy developed hindquarter weakness after vaccination with a **multivalent vaccine**. This is suggestive of post-vaccinal polyradiculoneuritis. To date, only 1 similar case has been reported, which may be due to the under-reporting of suspected adverse drug reactions.

L46 ANSWER 42 OF 162 MEDLINE on STN
2001428188. PubMed ID: 11475904. The humoral immune response to recombinant nucleocapsid antigen of canine distemper virus in dogs vaccinated with attenuated distemper virus or DNA encoding the nucleocapsid of wild-type virus. Griot-Wenk M E; Cherpillod P; Koch A; Zurbriggen R; Bruckner L; Wittek R; Zurbriggen A. (Institute of Animal Neurology, Bremgartenstrasse 109a, University of Berne, 3012 Berne, Switzerland.. mgriot-wenk@healthecon.com) . Journal of veterinary medicine. A, Physiology, pathology, clinical medicine, (2001 Jun) 48 (5) 295-302. Journal code: 100955112. ISSN: 0931-184X. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB This study compared the humoral immune response against the nucleocapsid-(N) protein of canine distemper virus (CDV) of dogs vaccinated with a **multivalent vaccine** against parvo-, adeno-, and parainfluenza virus and leptospira combined with either the attenuated CDV Onderstepoort strain (n = 15) or an expression plasmid containing the N-gene of CDV (n = 30). The vaccinations were applied intramuscularly three times at 2-week intervals beginning at the age of 6 weeks. None of the pre-immune sera recognized the recombinant N-protein, confirming the lack of maternal antibodies at this age. Immunization with DNA vaccine for CDV resulted in positive serum N-specific IgG response. However, their IgG (and IgA) titres were lower than those of CDV-vaccinated dogs. Likewise, DNA-vaccinated dogs did not show an IgM peak. There was no increase in N-specific serum IgE titres in either group. Serum titres to the other **multivalent vaccine** components were similar in both groups.

L46 ANSWER 43 OF 162 MEDLINE on STN
2001421897. PubMed ID: 11243687. Field studies on equine influenza vaccination regimes in thoroughbred foals and yearlings. Cullinane A; Weld J; Osborne M; Nelly M; Mcbride C; Walsh C. (The Virology Unit, The Irish Equine Centre, Johnstown, Naas, Co. Kildare, Ireland.. acullinane@equine-centre.ie) . Veterinary journal (London, England : 1997), (2001 Mar) 161 (2) 174-85. Journal code: 9706281. ISSN: 1090-0233. Pub. country: England: United Kingdom. Language: English.

AB SUMMARY: The purpose of these studies was to examine the response of Thoroughbred foals and yearlings to different influenza vaccines and vaccination regimes. The horses' antibody levels against haemagglutinin, an established correlate of protection were measured by haemagglutination inhibition. The first study investigated the extent to which maternal

findings suggest that repeat vaccination in the face of maternal antibodies may induce tolerance as defined by serological testing. The second study compared the immune response elicited by a subunit immune stimulating complex (ISCOM) vaccine, an inactivated whole virus vaccine and the same product containing equine herpesviruses and equine reoviruses in addition to equine influenza virus. The monovalent vaccine induced a significantly better response than the ISCOM or the **multivalent vaccine**. The final study demonstrated that the inclusion of an additional booster vaccination, between the second and third vaccination recommended by the vaccine manufacturers and required under the rules of racing in certain countries, is of benefit to young horses. Since these studies were performed, several of the vaccines have been updated with more recent virus strains in line with WHO/OIE recommendations. However, the general principles investigated in the studies remain relevant to these vaccines.

L46 ANSWER 44 OF 162 MEDLINE on STN
2001421890. PubMed ID: 11243680. Salmonella pathogenesis and immunity: we need effective **multivalent vaccines**. Wallis T S. Veterinary journal (London, England : 1997), (2001 Mar) 161 (2) 104-6. Journal code: 9706281. ISSN: 1090-0233. Pub. country: England: United Kingdom. Language: English.

L46 ANSWER 45 OF 162 MEDLINE on STN
2001409099. PubMed ID: 11257380. Immunization of livestock with DNA vaccines: current studies and future prospects. van Drunen Littel-van den Hurk S; Loehr B I; Babiuk L A. (Veterinary Infectious Disease Organization, University of Saskatchewan, 120 Veterinary Rd., S7N 5E3, Saskatoon, SK, Canada.) Vaccine, (2001 Mar 21) 19 (17-19) 2474-9. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Early studies using DNA immunization suggest the potential benefits of this form of immunization including: long-lived immunity, a broad spectrum of immune responses (both cell-mediated immunity and humoral responses) and the simultaneous induction of immunity to a variety of pathogens through the use of **multivalent vaccines**. Using marine and cow models, we studied methods to enhance and direct the immune response to polynucleotide vaccines. We demonstrated the ability to modulate the magnitude and direction of the immune response by co-administration of plasmid encoded cytokines and antigen. Also, we clearly demonstrated that the cellular components (cytosolic, membrane-anchored, or extracellular) to which the expressed antigen is delivered determines the types of immune responses induced. Since induction of immunity at mucosal surfaces (route of entry for many pathogens) is critical to prevent infection, various methods of delivering polynucleotide vaccines to animals including mucosal surfaces have been attempted and are described as future prospects for improving immune responses by DNA vaccination.

L46 ANSWER 46 OF 162 MEDLINE on STN
2001409077. PubMed ID: 11257357. Recombinant measles viruses expressing heterologous antigens of mumps and simian immunodeficiency viruses. Wang Z; Hangartner L; Cornu T I; Martin L R; Zuniga A; Billeter M A; Naim H Y. (Institute of Molecular Biology, University of Zurich-Irchel, Winterthurerstrasse 190, 8057, Zurich, Switzerland.) Vaccine, (2001 Mar 21) 19 (17-19) 2329-36. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB We have genetically engineered a panel of recombinant measles viruses (rMVs) that express from various positions within the MV genome either the HN or F surface glycoproteins of mumps virus (MuV) or the env, gag or pol proteins from simian immunodeficiency virus (SIV). All rMVs were rescued from the respective antigenomic plasmid constructs; progeny viruses replicated comparably to the progenitor Edmonston B MV, but showed slight propagation retardation, which was dependent on the size and nature of the expressed proteins and on the genomic position of the inserts. All

transgenes except that encoding mumps F glycoprotein were faithfully maintained and expressed even after virus amplification by 10(20). Our results suggest possible applications of rMVs as live-attenuated, **multivalent vaccines** against retroviruses such as SIV and HIV as well as other pathogens more distantly related to MV than MuV.

L46 ANSWER 47 OF 162 MEDLINE on STN
2001405531. PubMed ID: 11456137. Can we eradicate rheumatic fever in the 21st century?. Stollerman G H. (Boston University, USA.. gstollerman@valley.net) . Indian heart journal, (2001 Jan-Feb) 53 (1) 25-34. Journal code: 0374675. ISSN: 0019-4832. Pub. country: India. Language: English.

AB In the latter half of the 20th century, the clinical importance of variation in the virulence of strains of GAS has been clearly demonstrated. Although still obscure, the pathogenesis of ARF requires immunologically significant infection of the throat by virulent GAS strains. These strains contain large hyaluronate capsules and large M-protein molecules. The latter contain epitopes cross-reactive with host tissues, and also contain superantigenic toxic moieties. In areas where ARF has become rare, GAS pharyngitis continues to be common but is caused predominantly by GAS strains of relatively low virulence. These, however, may colonize the throat avidly and stubbornly. Molecularly distinct pyoderma strains may cause acute glomerulonephritis, but they are not rheumatogenic even though they may secondarily infect the throat. In developing countries with a very high incidence of rheumatic heart disease, identification of the prevalent rheumatogenic GAS strains and development of a **multivalent vaccine** against them is currently an interesting strategy. Pending vaccine development, intense primary and secondary penicillin prophylaxis should continue to be sharply focused on populations with the highest prevalence of RHD as such measures may often succeed in driving away the most virulent rheumatogenic clones of GAS from their midst.

L46 ANSWER 48 OF 162 MEDLINE on STN
2001317644. PubMed ID: 11391160. Immunogenicity of recombinant envelope glycoproteins derived from T-cell line-adapted isolates or primary HIV isolates: a comparative study using **multivalent vaccine** approaches. Lemiale F; Brand D; Lebigot S; Verrier B; Buzelay L; Brunet S; Barin F. (Unite de Virologie, Equipe de Microbiologie Medicale et Moleculaire, Universite Francois Rabelais, Tours, France.) Journal of acquired immune deficiency syndromes (1999), (2001 Apr 15) 26 (5) 413-22. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB We investigated immunogenic properties of native envelope glycoproteins derived from HIV-1 (subtype B). Our main objective was to assess whether the design of **multivalent vaccines** affects generation of neutralizing antibodies against primary viruses. Recombinant Semliki Forest virus (SFV) particles producing various HIV-1 envelope glycoproteins were used as vaccine vectors. The following **multivalent vaccination** approaches were compared: 1) immunization with a mixture of recombinant SFV expressing envelope glycoproteins derived from three HIV-1 primary isolates and two T-cell laboratory-adapted (TCLA) viruses; 2) immunization with a mixture of recombinant SFV expressing only the envelope glycoproteins derived from three HIV-1 primary isolates; 3) sequential immunizations with the recombinant SFV expressing the envelope glycoproteins derived from three HIV-1 primary isolates and two TCLA viruses, respectively. Two monovalent vaccine approaches using SFV expressing envelope glycoproteins derived from a single primary isolate or TCLA virus were also included in the study. The **multivalent vaccination** strategies based on SFV vaccine vectors did not induce more neutralizing antibodies than the previously tested TCLA envelope immunogens, which gave disappointing results against primary isolates.

L46 ANSWER 49 OF 162 MEDLINE on STN
2001262068. PubMed ID: 11330183. Immunologic properties of coli surface antigen 6(CS6) of enterotoxigenic Escherichia coli and cholera toxin

Feng E L; Wang H L; Zhang Z S; Su G F; Huang C F. (Institute of Biotechnology, Beijing 100071, China.) Sheng wu gong cheng xue bao = Chinese journal of biotechnology, (2001 Jan) 17 (1) 29-33. Journal code: 9426463. ISSN: 1000-3061. Pub. country: China. Language: Chinese.

AB A host-plasmid balancing system composed with a delta asd mutant (FaD) of an avirulent strain (T32) of Shigella flexneri 2a and plasmid harboring asd gene was used to express enterotoxigenic E. coli surface antigen 6(CS6) and V. cholerae toxin subunit B (CTB). The results of Western blotting and ELISA showed that all of recombinant plasmids (pYX201, pYX202 and pYX203) could be maintained stably and expressed CS6 and CTB respectively in T32 without any antibiotic selection. All the recombinant bacterial strains could elicit the corresponding antibodies in rabbits. The antibodies against CTB elicited by both FaD/pYX201 and FaD/pYX203 showed to be high level, and had long prolongation time, in otherwise, the antibodies against CS6 showed to be low level, indicating that higher expression level of foreign antigen may be benefit for construction of genetic **multivalent vaccine**.

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     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

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                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

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                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
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L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
L28           7 S E8
L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37         138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38          10 S L37 AND DENDRITIC
L39           1 S L38 AND (GENE VACCINATION)
L40         181 S (NAKED PLASMID DNA)
L41          11 S L40 AND PY=1996
L42           5 S L40 AND DENDRITIC
L43           0 S L40 AND (MULTIVALENT)
L44          80 S MULTIVALENT VACCINE
L45           1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46         162 S MULTIVALEN? VACCIN?
L47           6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48           0 S L46 AND (TWO PLASMIDS)

=> s (multi-plasmid DNA vaccination)
         43670 MULTI
         54046 PLASMID
        741015 DNA
         62327 VACCINATION
L49          1 (MULTI-PLASMID DNA VACCINATION)
                 (MULTI(W)PLASMID(W)DNA(W)VACCINATION)

=> s (HIV or human immunodeficiency virus)
        136179 HIV
       8499030 HUMAN
        112830 IMMUNODEFICIENCY
        373673 VIRUS
         42682 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L50     140917 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l50 and vaccin?
        146418 VACCIN?
L51       7795 L50 AND VACCIN?

=> s l51 and (plasmid?)
         97133 PLASMID?
L52        324 L51 AND (PLASMID?)

=> s l52 and (polynucleotide or DNA or plasmid? or DNA-based or naked or DNA injection or genet
          3980 POLYNUCLEOTIDE
        741015 DNA
         97133 PLASMID?
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618735 BASED
1817 DNA-BASED
(DNA(W)BASED)
3530 NAKED
741015 DNA
225971 INJECTION
286 DNA INJECTION
(DNA(W)INJECTION)
485047 GENETIC
L53 324 L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NAKED OR DNA INJECTION OR GENETIC)

=> s l53 and (CTL or cytotoxic or class I)
11129 CTL
81743 CYTOTOXIC
171456 CLASS
1140219 I
32227 CLASS I
(CLASS(W)I)
L54 132 L53 AND (CTL OR CYTOTOXIC OR CLASS I)

=> d l54,cbib,ab,100-132

L54 ANSWER 100 OF 132 MEDLINE on STN
1998222345. PubMed ID: 9561560. Study of the immunogenicity of different recombinant Mengo viruses expressing HIV1 and SIV epitopes. Van der Ryst E; Nakasone T; Habel A; Venet A; Gomard E; Altmeyer R; Girard M; Borman A M. (Unite de Virologie moleculaire, Institut Pasteur, Paris.) Research in virology, (1998 Jan-Feb) 149 (1) 5-20. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Recombinant Mengo viruses expressing heterologous genes have proven to be safe and immunogenic in both mice and primates, and to be able to induce both humoral and cellular immune responses (Altmeyer et al., 1995, 1996). Several recombinant Mengo viruses expressing either a large region (aa 65-206) of the HIV1 nef gene product, or **cytotoxic** T lymphocyte (**CTL**) epitopic regions from the SIV Gag (aa 182-190), Nef (aa 155-178) and Pol (aa 587-601) gene products were engineered. The heterologous antigens were expressed either as fusion proteins with the Mengo virus leader (L) protein, or in cleaved form through autocatalytic cleavage by the foot-and-mouth disease virus 2A protein. Rhesus macaques and BALB/c mice inoculated with the Mengo virus SIV recombinants failed to develop **CTL** responses against the SIV gene products, while one of the **HIV**-Nef recombinants induced a weak **CTL** response in mice directed to an HIV1 Nef peptide spanning positions 182-198. In contrast, BALB/c mice immunized with **vaccinia** virus recombinants expressing HIV1 Nef developed a strong **CTL** response to the 182-198 peptide and also responded to a second peptide spanning positions 73-81. These results indicate that Mengo virus recombinants expressing HIV1 Nef and SIV **CTL** epitopes are weak immunogens. One of the fusion recombinants expressing SIV **CTL** epitopes failed to infect macaques even when used at high doses, while the recombinant expressing HIV1 Nef as a fusion protein failed to infect BALB/c mice. These results demonstrate that the expression of certain heterologous sequences as fusion proteins with L can result in the loss of the ability of the recombinant to infect normally susceptible animals.

L54 ANSWER 101 OF 132 MEDLINE on STN
1998214891. PubMed ID: 9554272. Induction of a TH1 type cellular immune response to the human immunodeficiency type 1 virus by in vivo **DNA** inoculation. Boyer J; Ugen K; Wang B; Chattergoon M; Tsai A; Merva M; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, USA.) Developments in biological standardization, (1998) 92 169-74. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB **DNA** inoculation is capable of producing antigens intracellularly for ultimate presentation to the cellular and humoral components of the immune

system and has potential for **vaccine** strategies against a number of infectious pathogens including **HIV**-1. It is well documented that the antigenic diversity of **HIV**-1 and its high level of nucleotide mutations during reverse transcription can lead to escape from immune surveillance. However, data suggest that a CD8-mediated **cytotoxic** T lymphocyte response may be less susceptible to escape mutants. We have shown previously that in vivo inoculation of rodents and non-human primates with **plasmid** expression vectors encoding **HIV**-1 gene products leads to production of **HIV**-1 antigens and results in the production of both cellular and humoral immune responses. In addition we have also demonstrated previously that these responses lead to protection in several in vivo models. We further demonstrate here that the cellular response induced is a type TH1 response and specific lysis of **HIV**-infected targets is CD8-mediated.

L54 ANSWER 102 OF 132 MEDLINE on STN
1998132000. PubMed ID: 9472658. Adjuvant effect of Ubenimex on a **DNA vaccine** for **HIV**-1. Sasaki S; Fukushima J; Hamajima K; Ishii N; Tsuji T; Xin K Q; Mohri H; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Yokohama, Japan.) Clinical and experimental immunology, (1998 Jan) 111 (1) 30-5. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Enhancement of **DNA vaccine** immunogenicity is a current topic of high priority in the field of applied immunology, especially as a means of controlling **HIV** infection. The adjuvant effect of Ubenimex (UBX), an anti-cancer immunomodulator, on a **DNA** AIDS **vaccine** which we developed was examined in a murine model. UBX was formulated into a preparation containing **DNA plasmids** encoding env and rev genes of **HIV**-1 strain III(B), and was inoculated intramuscularly into BALB/c mice. The sera obtained with this mixture had 2(3)-2(5) times higher specific IgG titres than those obtained without the use of the adjuvant. UBX also elicited both a stronger **HIV**-1-specific DTH reaction, as measured by the footpad swelling test, and stronger **cytotoxic** T lymphocyte activity, as assayed by the 51Cr-release method, compared with responses using **DNA** alone. The cytokine secretion profile of restimulated immune lymphoid cells showed that UBX raised IL-2 and interferon-gamma levels and decreased IL-4 production. **HIV**-1-specific immunoglobulin subtype analysis demonstrated that UBX stimulated IgG2a production but suppressed synthesis of IgG1 and IgE. These results indicate that activation of the T-helper type 1 subset was induced by UBX, suggesting a mechanism of immunomodulation mediated by this agent. We conclude that UBX acts as an immunologic adjuvant for **DNA vaccination** against **HIV**-1. UBX may be a suitable adjuvant for clinical use because of its lack of antigenicity and low toxicity.

L54 ANSWER 103 OF 132 MEDLINE on STN
1998129331. PubMed ID: 9469429. Delivery of multiple CD8 **cytotoxic** T cell epitopes by **DNA vaccination**. Thomson S A; Sherritt M A; Medveczky J; Elliott S L; Moss D J; Fernando G J; Brown L E; Suhrbier A. (The Cooperative Research Centre for Vaccine Technology, Queensland Institute of Medical Research, Brisbane, Australia.) Journal of immunology (Baltimore, Md. : 1950), (1998 Feb 15) 160 (4) 1717-23. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Development of CD8 alphabeta **CTL** epitope-based **vaccines** requires an effective strategy capable of co-delivering large numbers of **CTL** epitopes. Here we describe a **DNA plasmid** encoding a polyepitope or "polytope" protein, which contained multiple contiguous minimal murine **CTL** epitopes. Mice **vaccinated** with this **plasmid** made MHC-restricted **CTL** responses to each of the epitopes, and protective **CTL** were demonstrated in recombinant **vaccinia** virus, influenza virus, and tumor challenge models. **CTL** responses generated by polytope **DNA plasmid vaccination** lasted for 1 yr, could be enhanced by co-delivering a gene for granulocyte-macrophage CSF, and appeared to be induced in the absence of CD4 T cell-mediated help. The ability to deliver large numbers of **CTL** epitopes using relatively small polytope constructs and **DNA vaccination** technology should find application in the design of human epitope-based **CTL vaccines**, in particular in **vaccines** against EBV,

HIV, and certain cancers.

L54 ANSWER 104 OF 132 MEDLINE on STN
1998118456. PubMed ID: 9454704. In vivo induction of specific **cytotoxic** T lymphocytes in mice and rhesus macaques immunized with **DNA** vector encoding an **HIV** epitope fused with hepatitis B surface antigen. Le Borgne S; Mancini M; Le Grand R; Schleef M; Dormont D; Tiollais P; Riviere Y; Michel M L. (Unite de Virologie et Immunologie Cellulaire, URA CNRS 1157, Paris, France.) Virology, (1998 Jan 20) 240 (2) 304-15. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **DNA** immunization offers a novel means to induce humoral and cellular immunity in inbred or in outbred animals. Here we have tested the efficiency of **genetic** immunization with hepatitis B virus (HBV) envelope-based vectors. In naive primates, injection of a **plasmid DNA** encoding HBV envelope proteins induced an HBV-specific **cytotoxic** response and appearance of potentially protective anti-HBs antibodies. Moreover, intramuscular and intradermal injections of a **DNA** expression vector encoding an epitope of the **human immunodeficiency virus** envelope fused to the surface protein of the hepatitis B virus (HBsAg) induced strong humoral and **cytotoxic** responses to antigenic determinants of both viruses in mice and nonhuman primates alike. In addition, in protein-primed Rhesus monkeys B-cell memory was successfully boosted by **DNA injection** of hybrid vectors and animals subsequently developed a multispecific cellular response. This suggests that **DNA-based** immunization could be used to boost efficiently and broaden the immune response in individuals immunized with conventional **vaccines**, regardless of their **genetic** variability. These results also indicate that it might be possible to rationally design HBsAg-based expression vectors to induce multispecific immune responses for **vaccination** against hepatitis B and other pathogens.

L54 ANSWER 105 OF 132 MEDLINE on STN
1998022620. PubMed ID: 9359662. Cationic liposomes are a strong adjuvant for a **DNA vaccine** of **human immunodeficiency virus** type 1. Ishii N; Fukushima J; Kaneko T; Okada E; Tani K; Tanaka S I; Hamajima K; Xin K Q; Kawamoto S; Koff W; Nishioka K; Yasuda T; Okuda K. (Department of Dermatology, Yokohama City University School of Medicine, Yokohama, Japan.) AIDS research and human retroviruses, (1997 Nov 1) 13 (16) 1421-8. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Liposomes have been widely used to enhance the immune response. In the present investigation, we studied their in vivo immunomodulation of an **HIV**-1-specific **DNA vaccine** candidate (pCMV160/REV) constructed with the cytomegalovirus (CMV) promoter-conjugated **HIV**-1 env and rev **DNA plasmids**. By immunizing with pCMV160/REV and cationic liposomes through various routes (intramuscular, intraperitoneal, subcutaneous, intradermal, and intranasal), we induced higher levels of both antibody production and delayed-type hypersensitivity (DTH) than by using **DNA vaccine** alone. The **HIV**-1-specific **cytotoxic** T lymphocyte (**CTL**) activity was observed to be stronger on immunization with the **DNA vaccine** and cationic liposome combination. The intramuscular, intraperitoneal, and intranasal inoculation routes were more effective in inducing strong DTH and antibody responses than the subcutaneous and intradermal routes. Taken together, these results suggest that cationic liposomes can be highly effective when used with **DNA vaccines** and administered by various routes.

L54 ANSWER 106 OF 132 MEDLINE on STN
97456556. PubMed ID: 9311870. Virus-specific **cytotoxic** T-lymphocyte activity elicited by coimmunization with **human immunodeficiency virus** type 1 genes regulated by the bacteriophage T7 promoter and T7 RNA polymerase protein. Selby M J; Doe B; Walker C M. (Chiron Corporation, Emeryville, California 94608, USA.) Journal of virology, (1997 Oct) 71 (10) 7827-31. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

with **DNA plasmids** containing the **human immunodeficiency virus** type 1 (**HIV**-1) gp120 envelope (pTMIgp120) or p55gag (pTMIgag) gene regulated by the bacteriophage T7 promoter. Immunization with either **plasmid** resulted in **CTL** activity against **class I** major histocompatibility complex-restricted viral epitopes when coadministered with a recombinant **vaccinia** virus expressing the T7 RNA polymerase protein (T7 RNAP) but not a control **vaccinia** virus. Recombinant **vaccinia**-T7 RNAP virus (VTF7-3) could be replaced with a noninfectious source of T7 RNAP. A three-component **vaccine** consisting of pTMIgag, a recombinant subunit T7 RNAP protein, and a **plasmid** (pT7T7) encoding T7 RNAP under the control of its own promoter induced gag-specific **CTL** activity. Intramuscular immunization with the pTMIgag **plasmid** delivered with either the T7 RNAP protein or pT7T7 **plasmid** alone also induced **HIV**-1-specific **CTL**. Thus, there is adventitious expression of the pT7T7 **plasmid** in vivo, and enough T7 RNAP is produced to result in production of p24gag protein from the pTMIgag **plasmid**. The results demonstrate that regulated expression of genes in vivo is possible with this T7-based expression system, and may be useful in **vaccine** settings where short-term cytoplasmic expression of protein in antigen presenting cells is desired.

L54 ANSWER 107 OF 132 MEDLINE on STN

97404403. PubMed ID: 9256490. Potent, protective anti-**HIV** immune responses generated by bimodal **HIV** envelope **DNA** plus protein **vaccination**. Letvin N L; Montefiori D C; Yasutomi Y; Perry H C; Davies M E; Lekutis C; Alroy M; Freed D C; Lord C I; Handt L K; Liu M A; Shiver J W. (Harvard Medical School, Beth Israel Hospital, Boston, MA 02215, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1997 Aug 19) 94 (17) 9378-83. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB It is generally thought that an effective **vaccine** to prevent **HIV**-1 infection should elicit both strong neutralizing antibody and **cytotoxic** T lymphocyte responses. We recently demonstrated that potent, boostable, long-lived **HIV**-1 envelope (Env)-specific **cytotoxic** T lymphocyte responses can be elicited in rhesus monkeys using **plasmid**-encoded **HIV**-1 env **DNA** as the immunogen. In the present study, we show that the addition of **HIV**-1 Env protein to this regimen as a boosting immunogen generates a high titer neutralizing antibody response in this nonhuman primate species. Moreover, we demonstrate in a pilot study that immunization with **HIV**-1 env **DNA** (multiple doses) followed by a final immunization with **HIV**-1 env **DNA** plus **HIV**-1 Env protein (env gene from HXBc2 clone of **HIV** IIIB; Env protein from parental **HIV** IIIB) completely protects monkeys from infection after i.v. challenge with a chimeric virus expressing **HIV**-1 env (HXBc2) on a simian immmunodeficiency virusmac backbone (SHIV-HXBc2). The potent immunity and protection seen in these pilot experiments suggest that a **DNA** prime/**DNA** plus protein boost regimen warrants active investigation as a **vaccine** strategy to prevent **HIV**-1 infection.

L54 ANSWER 108 OF 132 MEDLINE on STN

97378953. PubMed ID: 9234550. Nucleic acid immunization of chimpanzees as a prophylactic/immunotherapeutic **vaccination** model for **HIV**-1: prelude to a clinical trial. Ugen K E; Boyer J D; Wang B; Bagarazzi M; Javadian A; Frost P; Merva M M; Agadjanyan M G; Nyland S; Williams W V; Coney L; Ciccarelli R; Weiner D B. (Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, Tampa 33612, USA.) Vaccine, (1997 Jun) 15 (8) 927-30. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Vaccine** development strategies have often utilized recombinant envelope glycoproteins which usually generate strong humoral immune responses but which do not generate strong **cytotoxic** T lymphocytes (**CTL**). A recent novel experimental **vaccination** approach involves the technology known as nucleic acid immunization in which **DNA plasmids** expressing a gene of interest is injected intramuscularly in experimental animals. These expressed proteins then are presented to the immune system with the

subsequent development of strong antibody and cellular (particularly **CTL**) immune responses. These types of immune responses have been elicited in rodents as well as nonhuman primates including chimpanzees. Results from studies on nucleic acid immunization of **HIV**-1 infected chimpanzees with envelope glycoprotein expressing constructs indicated that this method was able to decrease substantially **HIV**-1 viral load in these chimpanzees. These data are useful for the development and implementation of human phase I clinical trials with **HIV** constructs expressing various genes from the **HIV**-1 genome.

L54 ANSWER 109 OF 132 MEDLINE on STN
97378942. PubMed ID: 9234539. Anti-**HIV** env immunities elicited by nucleic acid **vaccines**. Shiver J W; Davies M E; Yasutomi Y; Perry H C; Freed D C; Letvin N L; Liu M A. (Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA.) Vaccine, (1997 Jun) 15 (8) 884-7. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Plasmid DNA vaccines** encoding **HIV**-1 env were used to immunize mice and nonhuman primates. **Plasmids** were prepared that produced either secreted gp120 or full-length gp160. Mice immunized with gp120 **DNA** developed strong antigen-specific antibody responses, CD8+ **cytotoxic** T lymphocytes (**CTL**) (following in vitro restimulation with gp120-derived peptide), and showed in vitro proliferation and Th1-like cytokine secretion [gamma-interferon, interleukin (IL)-2 with little or no IL-4] by lymphocytes obtained from all lymphatic compartments tested (spleen, blood, and inguinal, iliac, and mesenteric lymph nodes). This indicated that systemic anti-gp120 cell-mediated immunity was induced by this **DNA vaccine**. Although similar antibody responses were observed in mice immunized by either intramuscular or intradermal routes, T cell responses were significantly stronger in mice injected intramuscularly. Rhesus monkeys immunized with both gp120 and gp160 DNAs exhibited significant CD8+ **CTL** responses, following in vitro restimulation of peripheral blood lymphocytes with antigen. These experiments demonstrate that **DNA** immunization elicits potent immune responses against **HIV** env in both a rodent and a nonhuman primate species.

L54 ANSWER 110 OF 132 MEDLINE on STN
97378941. PubMed ID: 9234538. Development of a multicomponent candidate **vaccine** for **HIV**-1. Kim J J; Ayyavoo V; Bagarazzi M L; Chattergoon M; Boyer J D; Wang B; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Vaccine, (1997 Jun) 15 (8) 879-83. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Nucleic acid or **DNA** immunization represents a novel approach to both **vaccine** and immune therapeutic development. **DNA vaccination** induces antigen-specific cellular and humoral immune responses through the delivery of non-replicating transcription units which drive the synthesis of specific foreign proteins within the inoculated host. We have previously reported on the potential use of **DNA** immunization as a novel **vaccine** strategy for **HIV**-1. We found that both antigen-specific cellular and humoral immune responses could be induced in vivo with various **DNA vaccine** constructs against different antigenic targets within **HIV**-1. In order to enhance the **DNA vaccine**'s ability to elicit cell-mediated immune responses, we co-delivered **plasmids** encoding costimulatory molecule B7 and interleukin-12 genes with **DNA vaccine** for **HIV**-1. We observed a dramatic increase in both antigen-specific T helper cell proliferation and **CTL** response. Eventual development of successful **vaccines** for **HIV**-1 would likely involve targeting multiple antigenic components of the virus to direct and empower the immune system to protect the host from viral infection. We present here the utility of multicomponent **DNA** immunization to elicit specific humoral and cell-mediated immune responses against different antigenic targets of **HIV**-1 as well as the ability of this immunization strategy to achieve significant enhancements of antigen-specific cellular immune responses.

L54 ANSWER 111 OF 132 MEDLINE on STN

induces immune responses that are boosted by a recombinant gp120 protein subunit. Barnett S W; Rajasekar S; Legg H; Doe B; Fuller D H; Haynes J R; Walker C M; Steimer K S. (Geniva Inc. Middleton, WI 53562, USA.) Vaccine, (1997 Jun) 15 (8) 869-73. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Small animals were immunized with **plasmid DNA** encoding **HIV**-1 envelope gp120 either intramuscularly by needle injection (mice and guinea pigs) or epidermally with the Accell gene gun (guinea pits). Subsequently, the animals were boosted with a recombinant gp120 protein subunit **vaccine** in an oil-in-water based adjuvant, MF59. Antibodies and **cytotoxic** T-lymphocyte (**CTL**) immune responses to the **HIV** envelope glycoprotein were observed in animals immunized with gp120 **DNA** derived from the **HIV**-1SF2 laboratory strain or from **HIV**-1 field isolates. Titers of ELISA antibodies and serum neutralizing antibodies against the **HIV**-1SF2 laboratory isolate were substantially increased in **DNA**-immunized animals following a single boost with recombinant gp120 protein subunit. This **DNA** prime/protein subunit boost immunization approach may be important for **vaccination** against infectious agents such as **HIV** for which it is difficult to raise strong antiviral humoral responses with **DNA vaccination** alone.

L54 ANSWER 112 OF 132 MEDLINE on STN

97362802. PubMed ID: 9219266. Engineering of in vivo immune responses to **DNA** immunization via codelivery of costimulatory molecule genes. Kim J J; Bagarazzi M L; Trivedi N; Hu Y; Kazahaya K; Wilson D M; Ciccarelli R; Chattergoon M A; Dang K; Mahalingam S; Chalian A A; Agadjanyan M G; Boyer J D; Wang B; Weiner D B. (Department of Chemical Engineering, University of Pennsylvania, Philadelphia 19104, USA.) Nature biotechnology, (1997 Jul) 15 (7) 641-6. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB Nucleic acid immunization is a novel **vaccination** technique to induce antigen-specific immune responses. We have developed expression cassettes for cell surface markers CD80 and CD86, two functionally related costimulatory molecules that play an important role in the induction of T cell-mediated immune responses. Coimmunization of these expression **plasmids**, along with **plasmid DNA** encoding for **HIV**-1 antigens, did not result in any significant change in the humoral response; however, we observed a dramatic increase in **cytotoxic** T-lymphocyte (**CTL**) induction as well as T-helper cell proliferation after the coadministration of CD86 genes. In contrast, coimmunization with a CD80 expression cassette resulted in a minor, but positive increase in T-helper cell or **CTL** responses. This strategy may be of value for the generation of rationally designed **vaccines** and immune therapeutics.

L54 ANSWER 113 OF 132 MEDLINE on STN

97288401. PubMed ID: 9143379. Strong augment effect of IL-12 expression **plasmid** on the induction of **HIV**-specific **cytotoxic** T lymphocyte activity by a peptide **vaccine** candidate. Hamajima K; Fukushima J; Bukawa H; Kaneko T; Tsuji T; Asakura Y; Sasaki S; Xin K Q; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) Clinical immunology and immunopathology, (1997 May) 83 (2) 179-84. Journal code: 0356637. ISSN: 0090-1229. Pub. country: United States. Language: English.

AB We previously reported that repeated inoculation of VC1, a macromolecular multicomponent peptide **vaccine** emulsified with Freund's adjuvant (VC1-F), induced high **cytotoxic** T lymphocyte (**CTL**) levels and a substantial level of multivalent antibodies which neutralized various **human immunodeficiency virus** type 1 (**HIV**-1) isolates. In the present study, we report that inoculation of VC1-F plus interleukin (IL)-12 expression **plasmid** can induce a higher antigen-specific **CTL** response compared to that with VC1-F alone. VC1-F plus IL-12 expression **plasmid** or VC1-F alone were inoculated to BALB/c mice twice at interval of 2 weeks. Two weeks after the second inoculation, spleen effector cells from these mice were examined. Stronger **CTL** responses against target cells were observed from the inoculation of VC1-F plus IL-12 **plasmid**

induction. The inoculation of VC1 plus IL-12 **plasmid** also produced higher **CTL** activity than the inoculation of VC1 alone. These augmented **CTL** activities were not observed using target cells pulsed with non-**HIV**-specific peptides and different **class I** haplotype cells. These data demonstrate that co-inoculation of cell-mediated immune potent antigen and IL-12 **plasmids** can enhance the antigen-specific **CTL** response. This may be a potential approach for the induction of cellular immunization against **HIV**-1 and other diseases.

L54 ANSWER 114 OF 132 MEDLINE on STN
97272168. PubMed ID: 9127013. **HIV**-1 env **DNA vaccine** administered to rhesus monkeys elicits MHC class II-restricted CD4+ T helper cells that secrete IFN-gamma and TNF-alpha. Lekutis C; Shiver J W; Liu M A; Letvin N L. (Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.. clekutis@bidmc.harvard.edu) . Journal of immunology (Baltimore, Md. : 1950), (1997 May 1) 158 (9) 4471-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The Th cell response elicited by an **HIV**-1 env **plasmid DNA vaccine** was assessed in rhesus monkeys by isolation of gp120-specific, MHC class II-restricted CD4+ T cell lines from PBL of **vaccinated** animals. The Env-specific CD4+ T cell lines recognized epitopes located in the second hypervariable region and in the carboxyl terminus of **HIV**-1 gp120. These cell lines proliferated in response to APC in the presence of recombinant gp120, as well as to APC expressing virally encoded Env. All of the CD4+ T cell lines responded to Env peptide by secreting IFN-gamma and TNF-alpha without appreciable IL-4 production. Recombinant gp120 stimulation of PBL from these **vaccinated** monkeys elicited the secretion of a similar profile of cytokines. Demonstration of a nucleotide **vaccine** eliciting a Th1-like immune response is consistent with the well documented ability of **naked DNA vaccines** to induce durable CD8+ **CTL** responses.

L54 ANSWER 115 OF 132 MEDLINE on STN
97256631. PubMed ID: 9103472. Enhancement of cell-mediated immunity against **HIV**-1 induced by coinnoculation of **plasmid**-encoded **HIV**-1 antigen with **plasmid** expressing IL-12. Tsuji T; Hamajima K; Fukushima J; Xin K Q; Ishii N; Aoki I; Ishigatsubo Y; Tani K; Kawamoto S; Nitta Y; Miyazaki J; Koff W C; Okubo T; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Kanazawa-ku, Yokohama, Japan.) Journal of immunology (Baltimore, Md. : 1950), (1997 Apr 15) 158 (8) 4008-13. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Previous investigations have demonstrated that **CTL** may play an important role in suppressing the disease progression of **HIV** infection. In this study, we inoculated mice with IL-12 expression **plasmid** together with **plasmid**-encoding **HIV**-1 envelope to enhance **CTL** activity by activating a Th1-type response. The results of delayed-type hypersensitivity using the footpad swelling response and of **CTL** activity clearly showed that **HIV**-1-specific cell-mediated immunity was enhanced by inoculation of the IL-12 expression **plasmid**. Quantitation of cytokine in the sera of IL-12-inoculated mice revealed that IFN-gamma significantly increased. The enhanced cell-mediated immunity responses were abrogated by combined administration of the IL-12 expression **plasmid** and neutralizing anti-IFN-gamma Ab. Together, these results suggest that enhanced virus-specific cell-mediated immunity occurred via an endogenously produced IFN-gamma by inoculation of IL-12 expression **plasmid**.

L54 ANSWER 116 OF 132 MEDLINE on STN
97234548. PubMed ID: 9079822. Immunomodulatory effects of a **plasmid** expressing B7-2 on **human immunodeficiency virus**-1-specific cell-mediated immunity induced by a **plasmid** encoding the viral antigen. Tsuji T; Hamajima K; Ishii N; Aoki I; Fukushima J; Xin K Q; Kawamoto S; Sasaki S; Matsunaga K; Ishigatsubo Y; Tani K; Okubo T; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) European journal of immunology, (1997 Mar) 27 (3) 782-7. Journal

Republic of. Language: English.

AB B7 co-stimulation is essential for activating resting T cells following antigen recognition by the T cell receptor. To determine whether B7 has adjuvant activities on **human immunodeficiency virus** type-1 (**HIV**-1)-specific immunity induced by inoculation of a **plasmid** encoding **HIV**-1 env and rev (**DNA vaccine**), B7-1 and B7-2 expression **plasmids** were co-inoculated with the **DNA vaccine**. The delayed-type hypersensitivity response and **cytotoxic** T lymphocyte (**CTL**) activity were significantly enhanced when B7-2 expression **plasmid** was co-inoculated with the **DNA vaccine**, but were unaffected when the B7-1 expression **plasmid** was used with the **vaccine** instead. The immunological response enhanced by B7-2 decreased below the level of mice immunized with the **DNA vaccine** in combination with CTLA4Ig, an inhibitor of the B7/CD28 co-stimulatory signal, suggesting that this signal is critical for the enhanced response induced by co-inoculation of the **DNA vaccine** and B7-2 expression **plasmid**. This enhancement appeared to occur via an interferon-gamma (IFN-gamma)-dependent mechanism, as combined administration of the B7-2 **plasmid** and neutralizing anti-IFN-gamma antibody abrogated the virus-specific cell-mediated immunity. These results suggest that this gene-based co-inoculation strategy using **HIV**-1 viral antigen and B7-2 co-stimulatory molecule could be a powerful means of combating **HIV**-1 infection.

L54 ANSWER 117 OF 132 MEDLINE on STN

97217373. PubMed ID: 9120397. Targeting of **HIV**-1 antigens for rapid intracellular degradation enhances **cytotoxic** T lymphocyte (**CTL**) recognition and the induction of de novo **CTL** responses in vivo after immunization. Tobery T W; Siliciano R F. (Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.) Journal of experimental medicine, (1997 Mar 3) 185 (5) 909-20. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB CD8+ **cytotoxic** T lymphocytes (CTLs) have the ability to recognize and eliminate virally infected cells before new virions are produced within that cell. Therefore, a rapid and vigorous CD8+ **CTL** response, induced by **vaccination**, can, in principle, prevent disseminated infection in **vaccinated** individuals who are exposed to the relevant virus. There has thus been interest in novel **vaccine** strategies that will enhance the induction of CD8+ CTLs. In this study, we have tested the hypothesis that targeting an antigen to undergo more efficient processing by the **class I** processing pathway will elicit a more vigorous CD8+ **CTL** response against that antigen. Targeting a type I transmembrane protein, the **HIV**-1 envelope (env) protein, for expression in the cytoplasm, rather than allowing its normal co-translational translocation into the endoplasmic reticulum, sensitized target cells expressing this mutant more rapidly for lysis by an env-specific **CTL** clone. Additionally, a greatly enhanced de novo env-specific **CTL** response was induced in vivo after immunization of mice with recombinant **vaccinia** vectors expressing the cytoplasmic env mutant. Similarly, targeting a cytoplasmic protein, **HIV**-1 nef, to undergo rapid cytoplasmic degradation induced a greatly enhanced de novo nef-specific CD8+ **CTL** response in vivo after immunization of mice with either recombinant **vaccinia** vectors or **DNA** expression **plasmids** expressing the degradation targeted nef mutant. The targeting of viral antigens for rapid cytoplasmic degradation represents a novel and highly effective **vaccine** strategy for the induction of enhanced de novo **CTL** responses in vivo.

L54 ANSWER 118 OF 132 MEDLINE on STN

97190746. PubMed ID: 9038705. **HIV**-1-specific cell-mediated immunity is enhanced by co-inoculation of TCA3 expression **plasmid** with **DNA vaccine**. Tsuji T; Fukushima J; Hamajima K; Ishii N; Aoki I; Bukawa H; Ishigatsubo Y; Tani K; Okubo T; Dorf M E; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) Immunology, (1997 Jan) 90 (1) 1-6. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

we developed a candidate DNA vaccine designated pCMV160IIIB with pCMV (pCMV160IIIB/REV) that encodes gp160 of **human immunodeficiency virus** (**HIV**)-1IIIB and Rev driven by the cytomegalovirus (CMV) promotor. This **vaccine** induced both **HIV**-1-specific antibodies and **cytotoxic** T lymphocyte (**CTL**) activity. In the present study, we inoculated the TCA3 expression **plasmid** into mouse skeletal muscle with pCMV160IIIB/REV to determine whether this cytokine expression **plasmid** was able to modify the immune response. Results of a delayed-type hypersensitivity (DTH) assay using footpad swelling as well as those of a **CTL** assay clearly demonstrated that cell-mediated immunity (CMI) elicited by co-inoculation of pCMV160IIIB/REV with the TCA3 expression **plasmid** was markedly enhanced compared with that obtained using pCMV160IIIB/REV alone. When TCA3 expression **plasmid** was inoculated with anti-TCA3 antibody, enhancement of the DTH response was suppressed below the level of that obtained with pCMV160IIIB/REV alone. The titre of **HIV**-1-specific IgG2a was slightly high when pCMV160IIIB/REV was co-inoculated with this **plasmid**, suggesting that T-helper 1 (Th1) response was predominant in TCA3-inoculated mice. Infiltration of mononuclear cells was seen in the muscles at sites where TCA3 expression **plasmid** had been inoculated. Our present data suggest that TCA3 expression **plasmid** has potent adjuvant activity that results in an augmented CMI response.

L54 ANSWER 119 OF 132 MEDLINE on STN
97120475. PubMed ID: 8961146. Humoral and cellular immunities elicited by **HIV**-1 **vaccination**. Shiver J W; Davies M E; Perry H C; Freed D C; Liu M A. (Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA.) Journal of pharmaceutical sciences, (1996 Dec) 85 (12) 1317-24. Journal code: 2985195R. ISSN: 0022-3549. Pub. country: United States. Language: English.

AB Recently it has been shown that immunization with **plasmid DNA** encoding genes for viral or bacterial antigens can elicit both humoral and cellular immune responses in rodents and nonhuman primates. In this study, mice and nonhuman primates were **vaccinated** by intramuscular injection with **plasmids** that express either a secreted form of **HIV**-1 gp120 or rev proteins. Mice receiving the tPA-gp120 **DNA** developed antigen-specific antibody responses against recombinant gp120 protein and the V2 peptide neutralization epitope as determined by ELISA. **Vaccinated** mice also exhibited gp120-specific T cell responses, such as in vitro proliferation of splenocytes and MHC **Class I**-restricted **cytotoxic** T lymphocyte (**CTL**) activities, following antigen restimulation. In addition, supernatants from these lymphocyte cultures showed high levels of gamma-interferon production compared with IL-4, suggesting that primarily type 1-like helper T (Th1) lymphocyte responses were induced by both **vaccines**. Th1-like responses were also obtained for mice **vaccinated** with rev **DNA**. Immune responses induced by gp120 or rev **vaccines** were dose-dependent, boostable, and long-lived (> or = 6 months). Nonhuman primates **vaccinated** with tPA-gp120 **DNA** also showed antigen-specific T lymphocyte proliferative and humoral responses, including moderate levels of neutralizing sera against homologous **HIV**. These results suggest that **plasmid DNA** may provide a powerful means for eliciting humoral and cellular immune responses against **HIV**.

L54 ANSWER 120 OF 132 MEDLINE on STN
97047895. PubMed ID: 8892736. Induction of **HIV**-1 Nef-specific **cytotoxic** T lymphocytes by Nef-expressing **DNA vaccine**. Asakura Y; Hamajima K; Fukushima J; Mohri H; Okubo T; Okuda K. (First Department of Internal Medicine, Yokohama City University School of Medicine, Japan.) American journal of hematology, (1996 Oct) 53 (2) 116-7. Journal code: 7610369. ISSN: 0361-8609. Pub. country: United States. Language: English.

AB Recently, some individuals who have remained seronegative despite definite exposure to **HIV**-1 have been reported. Among these individuals, an unusually high frequency of **HIV**-1 Nef-specific **cytotoxic** T lymphocytes was observed. Direct injection of **plasmid DNA** encoding foreign antigen can elicit both cell-mediated immunity and antibody responses (**DNA vaccine**). We constructed an **HIV**-1 Nef-expressing **plasmid**, and we induced **HIV**-1 Nef-specific **cytotoxic** T lymphocytes. This is

the first report of inducing HIV-1 Nef specific cytotoxic T lymphocytes by **DNA vaccine**.

L54 ANSWER 121 OF 132 MEDLINE on STN
97047126. PubMed ID: 8892046. In vivo protective anti-**HIV** immune responses in non-human primates through **DNA** immunization. Boyer J D; Wang B; Ugen K E; Agadjanyan M; Javadian A; Frost P; Dang K; Carrano R A; Ciccarelli R; Coney L; Williams W V; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Journal of medical primatology, (1996 Jun) 25 (3) 242-50. Journal code: 0320626. ISSN: 0047-2565. Pub. country: Denmark. Language: English.

AB An effective immune response involves the specific recognition of and elimination of an infectious organism at multiple levels. In this context **DNA** immunization can present functional antigenic proteins to the host for recognition by all arms of the immune system, yet provides the opportunity to delete any genes of the infectious organism which code for antigens or pieces of antigens that may have deleterious effects. Our group has developed the use of nucleic acid immunization as a possible method of **vaccination** against **Human immunodeficiency virus** type 1 (**HIV**-1) [1,2,3,10,11,12]. Sera from non-human primates immunized with **DNA** vectors that express the envelope proteins from **HIV**-1 contain antibodies specific to the **HIV**-1 envelope. These sera also neutralize **HIV**-1 infection in vitro and inhibit cell to cell infection in tissue culture. Analysis of cellular responses is equally encouraging. T cell proliferation as well as **cytotoxic** T cell lysis of relevant env expressing target cells were observed. In addition, evidence that **DNA vaccines** are capable of inducing a protective response against live virus was demonstrated using a chimeric SIV/**HIV** (SHIV) challenge in **vaccinated** cynomologous macaques. We found that nucleic acid **vaccination** induced protection from challenge in one out of four immunized cynomolgus macaques and viral load was lower in the **vaccinated** group of animals versus the control group of animals. These data encouraged us to analyze this **vaccination** technique in chimpanzees, the most closely related animal species to man. We observed the induction of both cellular and humoral immune responses with a **DNA vaccine** in chimpanzees. These studies demonstrate the utility of this technology to induce relevant immune responses in primates which may ultimately lead to effective **vaccines**.

L54 ANSWER 122 OF 132 MEDLINE on STN
96363710. PubMed ID: 8719522. Construction and immunogenicity of Salmonella typhimurium **vaccine** vectors that express **HIV**-1 gp120. Fouts T R; Tuskan R G; Chada S; Hone D M; Lewis G K. (Department of Geographic Medicine, School of Medicine, University of Maryland at Baltimore 21201, USA.) Vaccine, (1995 Dec) 13 (17) 1697-705. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Since the **human immunodeficiency virus** (**HIV**-1) is transmitted either parenterally or sexually, both mucosal and systemic immune responses may be required to provide protective immunity. Attenuated Salmonella vectors expressing heterologous antigen can stimulate responses in both compartments. To evaluate the utility of Salmonella vectors as an **HIV**-1 vector **vaccine**, a gene expression cassette encoding recombinant **HIV**-1 gp120 (rgp120) was integrated into the hisOGD locus of Salmonella typhimurium aroA strain, SL3261 (SL3261::120). To test if increased antigen expression potentiates immunogenicity, strains were constructed that express rgp120 from a multicopy asd-stabilized **plasmid** (SL7207 pYA:120). Immunoblot analysis demonstrated that SL7207 pYA:120 expressed approximately 50-fold more rgp120 than SL3261::120. Oral immunization of BALB/c mice with these strains did not stimulate an env-specific **CTL** response or a significant rise in antigp120 antibody titer as compared to controls. However, splenic T cells from SL7207 pYA::120 immunized mice proliferated upon restimulation with gp120 in vitro while splenocytes from SL3261::120 immunized mice did not, gp120 restimulated splenic T cells from SL7207 pYA:120 immune mice also produced IFN-gamma but no IL-5. Two conclusions can be drawn from these results. First, high level expression of rgp120 in Salmonella vectors is necessary to stimulate a gp120-specific

gp120-specific Th1 response in mice. This is the first report to describe the construction of a Salmonella::rgp120 vector **vaccine** that is immunogenic in mice.

L54 ANSWER 123 OF 132 MEDLINE on STN
96135359. PubMed ID: 8546392. **DNA** inoculation induces cross clade anti-**HIV**-1 responses. Wang B; Boyer J; Srikantan V; Ugen K; Agadjanian M; Merva M; Gilbert L; Dang K; McCallus D; Moelling K; +. (Apollon Inc., Malvern, Pennsylvania, USA.) Annals of the New York Academy of Sciences, (1995 Nov 27) 772 186-97. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Nucleic acid or **DNA** immunization represents a novel approach to **vaccine** and immune therapeutic development. The direct injection of expression cassettes into a living host results in in vivo gene expression and immune activation. In the case of **HIV**-1 it has been shown by our laboratory that facilitated injection mimicks aspects of live attenuated **vaccines** and that both humoral and cellular responses can be induced upon injection of a nucleic acid sequence directly into a host target tissue. Antisera from **HIV**-1 **plasmid** expression cassette-immunized animals contain anti-**HIV** envelope glycoprotein immune responses. The antiserum neutralizes **HIV**-1 infection and inhibits cell to cell infection in vitro. Cellular immune responses have also been evaluated. We observed both T cell proliferation and isotype switching consistent with the production of relevant T helper immune responses in immunized animals. Furthermore it was demonstrated that **CTL** lysis of relevant env-expressing targets was similarly induced. These studies further define the importance of evaluating this new technology for **vaccine** and immune therapeutic development for **HIV**-1 as well as for other human viral pathogens.

L54 ANSWER 124 OF 132 MEDLINE on STN
96099492. PubMed ID: 8523593. Simian immunodeficiency virus-specific **cytotoxic** T-lymphocyte induction through **DNA vaccination** of rhesus monkeys. Yasutomi Y; Robinson H L; Lu S; Mustafa F; Lekutis C; Arthos J; Mullins J I; Voss G; Manson K; Wyand M; Letvin N L. (Division of Viral Pathogenesis, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.) Journal of virology, (1996 Jan) 70 (1) 678-81. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In view of the growing evidence that virus-specific **cytotoxic** T lymphocytes (**CTL**) play an important role in containing the early spread of **human immunodeficiency virus** type 1 (**HIV**-1) in infected individuals, novel **vaccine** strategies capable of eliciting **HIV**-1-specific **CTL** are being pursued in attempts to create an effective AIDS **vaccine**. We have used the simian immunodeficiency virus of macaques (SIVmac)/rhesus monkey model to explore the induction of AIDS virus-specific **CTL** responses by **DNA vaccination**. We found that the inoculation of rhesus monkeys with **plasmid DNA** encoding SIVmac Env and Gag elicited a persisting SIVmac-specific memory **CTL** response. These **CTL** were CD8+ and major histocompatibility complex **class I** restricted. These studies provide evidence for the potential utility of **DNA** inoculation as an approach to an **HIV**-1 **vaccine**.

L54 ANSWER 125 OF 132 MEDLINE on STN
96020094. PubMed ID: 7492440. Induction of potent humoral and cell-mediated immune responses following direct injection of **DNA** encoding the **HIV** type 1 env and rev gene products. Okuda K; Bukawa H; Hamajima K; Kawamoto S; Sekigawa K; Yamada Y; Tanaka S; Ishi N; Aoki I; Nakamura M. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) AIDS research and human retroviruses, (1995 Aug) 11 (8) 933-43. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **DNA vaccines** have the potential of giving rise to a potent cell-mediated immune response by inducing intracellular synthesis and subsequent antigenic presentation of encoded antigens. We have tested a

DNA vaccine specific for **human immunodeficiency virus** type 1
(**HIV**-1) by the injection of animals with expression **plasmids** encoding the **HIV**-1 envelope protein and the Rev regulatory protein. Injection of both **plasmids** into mice, rabbits, or macaques was found to induce high levels of specific antibodies capable of efficiently inhibiting both **HIV**-1 infection and envelope-mediated cell fusion. A readily detectable delayed-type hypersensitivity (DTH) response was demonstrable in injected mice and lymphocytes derived from these proliferated in response to an **HIV**-1 envelope V3 loop-specific peptide. Interestingly, the injected mice or macaques also developed a strong **cytotoxic** T lymphocyte (**CTL**) response against target cells pulsed with the V3 peptide. Taken together, these data demonstrate that injection of **HIV**-1 gene expression **plasmids** can induce potent humoral and cell-mediated immune responses and suggest that **DNA vaccines** may prove to be significantly beneficial as a means of immunizing against **HIV**-1.

L54 ANSWER 126 OF 132 MEDLINE on STN
95373127. PubMed ID: 7645204. Induction of humoral and cellular immune responses to the human immunodeficiency type 1 virus in nonhuman primates by in vivo **DNA** inoculation. Wang B; Boyer J; Srikantan V; Ugen K; Gilbert L; Phan C; Dang K; Merva M; Agadjanyan M G; Newman M; +. (Apollon, Inc., Malvern, Pennsylvania 19355, USA.) Virology, (1995 Aug 1) 211 (1) 102-12. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **DNA** inoculation has the potential to produce antigens in a native as well as a host-"customized" form for presentation to the immune system. As such this technology may have relevance for **vaccine**/immune therapeutic strategies for a variety of infectious pathogens. In rodents in vivo inoculation of **plasmid** expression vectors encoding **HIV**-1 gene products leads to production of **HIV**-1 antigens in vivo, resulting in the production of both cellular and humoral immune responses. In primates only preliminary studies of serology have been reported. Here we report further evaluation of this new technology as a method to induce humoral and particularly cellular immune responses against a human pathogen, the **HIV**-1 virus, in nonhuman primates. Following inoculation and boosting of animals with an **HIV** gp160 **plasmid** expression vector we observed the induction of neutralizing responses against two diverse **HIV**-1 isolates in 2 of 3 **vaccinated** animals. T cell proliferative responses to **HIV** antigens were also observed in all **plasmid**-inoculated animals and specific cross-reactive **cytotoxic** T lymphocyte responses were developed in **vaccinated** animals. This report establishes the ability of **DNA** inoculation to induce cellular immune responses in nonhuman primates and suggests that further investigation of this technology with regard to human **vaccine** or immune therapeutic development is therefore warranted.

L54 ANSWER 127 OF 132 MEDLINE on STN
95194703. PubMed ID: 7888198. A qualitative progression in **HIV** type 1 glycoprotein 120-specific **cytotoxic** cellular and humoral immune responses in mice receiving a **DNA-based** glycoprotein 120 **vaccine**. Fuller D H; Haynes J R. (Agracetus, Inc., Middleton, Wisconsin 53562.) AIDS research and human retroviruses, (1994 Nov) 10 (11) 1433-41. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The potential for eliciting humoral and **cytotoxic** T lymphocyte (**CTL**) responses to **HIV**-1 gp120 by gene gun-based **DNA** immunization in mice was examined. We speculated that the induction of de novo antigen production in the epidermis of BALB/c mice following particle bombardment-based gene delivery would result in both MHC **class I**- and class II-mediated antigen presentation for the elicitation of **CTL** and antibody responses, respectively. Following epidermal delivery of microgram quantities of an expression **plasmid**, gp120 production resulted in the appearance of MHC **class I**-restricted, CD8+ **CTL** responses. gp120-specific **CTL** responses peaked following a booster immunization, then declined with the appearance of gp120-specific IgG responses when additional booster immunizations were administered. This qualitative progression in the nature of gp120-specific immune responses with

subsequent immunizations was paralleled by a simultaneous shift in the interferon-gamma and interleukin 4 release profiles following antigen stimulation of splenocytes in vitro. The simultaneous shifts in immune responses and cytokine release profiles indicate that the progression of antigen-specific **CTL** and IgG responses in gp120 **DNA**-immunized mice may be mediated through changes in the in vivo production of cytokines, such as those associated with the Th1 and Th2 subsets of CD4+ cells.

L54 ANSWER 128 OF 132 MEDLINE on STN
95185114. PubMed ID: 7879423. Facilitated **DNA** inoculation induces anti-**HIV**-1 immunity in vivo. Coney L; Wang B; Ugen K E; Boyer J; McCallus D; Srikantan V; Agadjanyan M; Pachuk C J; Herold K; Merva M; +. (Apollon Inc., Malvern, PA 19355.) Vaccine, (1994 Dec) 12 (16) 1545-50. Ref: 22. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Vaccine** design against **HIV**-1 is complicated both by the latent aspects of lentiviral infection and the diversity of the virus. The type of **vaccine** approach used is therefore likely to be critically important. In general, **vaccination** strategies have relied on the use of live attenuated material or inactivated/subunit preparations as specific immunogens. Each of these methodologies has advantages and disadvantages in terms of the elicitation of broad cellular and humoral immune responses. Although most success has been achieved with live attenuated **vaccines**, there is a conceptual safety concern associated with the use of these **vaccines** for the prevention of human infections. In contrast, subunit or killed **vaccine** preparations enjoy advantages in preparation and conceptual safety; however, their ability to elicit broad immunity is more limited. In theory, inoculation of a **plasmid DNA** that supports in vivo expression of proteins, and therefore presentation of the processed protein antigen to the immune system, could be used to combine the features of a subunit **vaccine** and a live attenuated **vaccine**. We have designed a strategy for intramuscular **DNA** inoculation to elicit humoral and cellular immune responses against expressed **HIV** antigens. Uptake and expression are significantly enhanced if **DNA** is administered in conjunction with the facilitating agent bupivacaine-HCl. Using this technique we have demonstrated functional cellular and humoral immune responses against the majority of **HIV**-1 encoded antigens in both rodents and non-human primates.

L54 ANSWER 129 OF 132 MEDLINE on STN
95169513. PubMed ID: 7865332. Accell particle-mediated **DNA** immunization elicits humoral, **cytotoxic**, and protective immune responses. Haynes J R; Fuller D H; Eisenbraun M D; Ford M J; Pertmer T M. (Agracetus, Inc., Middleton, Wisconsin 53562.) AIDS research and human retroviruses, (1994) 10 Suppl 2 S43-5. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Accell particle-mediated gene delivery technology was employed for the intracellular delivery of antigen-encoding expression vectors in epidermal tissues in laboratory animals. Delivery of **plasmid DNA**-coated gold microparticles using the Accell gene delivery system resulted in de novo antigen expression in epidermal cells that stimulated the induction of antigen-specific humoral and **cytotoxic** cellular immune responses. Optimal **DNA** delivery conditions favoring maximal humoral responses required the delivery of 5 x 10(7) micron-sized gold particles containing 300 **plasmid** copies per particle (80 ng of vector total) into a 4-cm^2 area of abdominal skin. Comparison of immune responses between animals that received intramuscular injections of relatively large quantities of vector **DNA** (100 micrograms) and those that received intracellular deliveries of submicrogram quantities of the same **DNA** to the epidermis demonstrated that the latter approach was considerably more effective at eliciting strong humoral responses. In addition, **cytotoxic** cellular immune responses were elicited to **HIV**-1 gp120 following epidermal delivery of **HIV**-1 gp160 or gp120 expression constructs. A qualitative shift from predominantly **cytotoxic** cellular to predominantly humoral immune responses with continued immunization indicated the potential for optimizing delivery conditions to favor specifically one type of response

over the other.

L54 ANSWER 130 OF 132 MEDLINE on STN
94023450. PubMed ID: 7692575. Recombinant hepatitis B surface antigen as a carrier of **human immunodeficiency virus** epitopes. Michel M L; Mancini M; Schlienger K; Tiollais P. (Unite de Recombinaison et Expression genetique, INSERM-U.163, Institut Pasteur, Paris.) Research in virology, (1993 Jul-Aug) 144 (4) 263-7. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Eukaryotic cells transformed with a **plasmid** expression vector are able to synthesize and assemble HBsAg, a complex multimeric lipoprotein particle. Hybrid particles carrying HIV1 antigenic determinants were constructed and injected into monkeys. A complete immune response including neutralizing antibodies, proliferative and **cytotoxic** T-cell activities was obtained. Thus, such **HIV**/HBsAg hybrid particles could be a new approach to multivalent **vaccination**.

L54 ANSWER 131 OF 132 MEDLINE on STN
93271832. PubMed ID: 1845119. Development of BCG as a live recombinant vector system: potential use as an **HIV vaccine**. Fuerst T R; Stover C K; de la Cruz V F. (Department of Molecular Genetics, MedImmune, Inc., Gaithersburg, Maryland 20878.) Biotechnology therapeutics, (1991) 2 (1-2) 159-78. Journal code: 8918082. ISSN: 0898-2848. Pub. country: United States. Language: English.

AB Bacille Calmette-Guerin (BCG), a live attenuated tubercle bacillus, is currently the most widely used **vaccine** in the world. Because of its unique characteristics, including low toxicity, adjuvant potential, and long-lasting immunity, BCG represents a novel **vaccine** vehicle with which to deliver protective antigens of multiple pathogens. We have developed episomal and integrative expression vectors employing regulatory sequences of major BCG heat shock proteins for stable maintenance and expression of foreign antigens in BCG **vaccine** strains (22). Shuttle **plasmids** capable of autonomous replication in Escherichia coli and BCG were constructed with a **DNA** cassette containing a minimal replicon derived from the Mycobacterium fortuitum **plasmid** pAL5000. Efficient and stable chromosomal integration of recombinant **plasmids** into BCG was achieved using a **DNA** segment containing the mycobacteriophage L5 attachment site and integrase coding sequence. Using the BCG hsp60 and hsp70 stress gene promoters, we were able to express Escherchia coli beta-galactosidase to levels in excess of 10% of total cell protein. The major antigens of **HIV**-1 gag, pol, and env were also stably expressed using our vector systems. The recombinant BCG elicited long-lasting humoral and cellular immune responses to these antigens in mice. Antibody responses to beta-galactosidase using as few as 200 colony-forming units were detected 6 weeks after immunization, and titers (1:30,000) were sustained for more than 10 weeks. Cellular immune responses, of both **cytotoxic** T cell (**CTL**) and helper T lymphocytes, were detected to beta-galactosidase. **CTL** responses were also induced to the **HIV**-1 envelope protein. Thus, we have demonstrated stable recombinant antigen expression, processing, and presentation using our recombinant BCG vector system. This live recombinant vector system shows promise as a universally applicable and safe **vaccine** vehicle for protection against various infectious diseases.

L54 ANSWER 132 OF 132 MEDLINE on STN
92075347. PubMed ID: 1742081. Soluble CD4-PE40 is **cytotoxic** for a transfected mammalian cell line stably expressing the envelope protein of **human immunodeficiency virus** (**HIV**-1), and cytotoxicity is variably inhibited by the sera of **HIV**-1-infected patients. Pitts T W; Bohanon M J; Leach M F; McQuade T J; Marschke C K; Merritt J A; Wierenga W; Nicholas J A. (Department of Cancer and Infectious Diseases, Upjohn Laboratories, Kalamazoo, MI 49007.) AIDS research and human retroviruses, (1991 Sep) 7 (9) 741-50. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Sera were obtained from 50 individuals infected with **human immunodeficiency virus** type 1 or from **HIV**-1-uninfected individuals before or after **vaccination** with recombinant gp160. These sera were

chimeric Pseudomonas exotoxin hybrid protein, sCD4-PE40. For these studies, Chinese hamster ovary (CHO) cells were transfected with a chimeric **plasmid** encoding the tat, rev, and envelope genes of **HIV**-1 and a cell line was selected for stable expression of the envelope glycoproteins at the cell surface (CHO-env). Cytotoxicity of sCD4-PE40 for CHO-env in the presence or absence of added human serum was quantitated spectrophotometrically following enzymatic reduction of a tetrazolium bromide within the mitochondria of viable cells (MTT assay). Several **HIV**+ sera inhibited the **cytotoxic** activity of sCD4-PE40; the antagonist had properties consistent with those of immunoglobulins in that it was heat stable, absorbed by protein A, and reversible by increasing the concentration of sCD4-PE40. Of 15 **HIV**+ sera which strongly reacted with gp120, 11 (73%) also potently inhibited sCD4-PE40 cytotoxicity, and cytotoxicity was inhibited by sera from some **HIV**- individuals after, but not before, immunization with gp160. These data suggested a role for antibody to gp120 in the antagonistic activity. However, not all sera with antibody to gp120 antagonized sCD4-PE40 cytotoxicity and high levels of antagonist activity were frequently (40%) found in **HIV**+ sera lacking immunoblot-detectable antibody to gp120, or antibody to either CD4 or PE40. Grouping of the **HIV**+ sera according to the patients' absolute number of CD4+ cells revealed that the degree of inhibition of sCD4-PE40 cytotoxicity approached a Gaussian distribution, suggesting that persons with CD4+ cell counts between 200 and 700/mm3 may be more likely to possess significant levels of serum antagonist. This data have implications for the clinical development of sCD4-PE40 or other sCD4-based therapeutics in the management of **HIV**-1 infection.

=> d l54,cbib,ab,50-99

L54 ANSWER 50 OF 132 MEDLINE on STN

2001409102. PubMed ID: 11257383. Modulation of antigen-specific cellular immune responses to **DNA vaccination** in rhesus macaques through the use of IL-2, IFN-gamma, or IL-4 gene adjuvants. Kim J J; Yang J S; Manson K H; Weiner D B. (Viral Genomix, Inc., Philadelphia, PA 19104, USA.) Vaccine, (2001 Mar 21) 19 (17-19) 2496-505. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Extensive experiments have shown **DNA vaccines'** ability to elicit immune responses in vivo in a safe and well-tolerated manner in several model systems, including rodents and non-human primates. As the **DNA-based vaccine** and immunotherapy approaches are being explored in humans, significant efforts have also been focused on further improving the immune potency of this technology. One strategy to enhance immune responses for **DNA vaccines** is the use of molecular or **genetic** adjuvants. These molecular adjuvant constructs (which encodes for immunologically important molecules such as cytokines) can be co-administered along with **DNA vaccine** constructs. Once delivered, these adjuvants have shown to modulate the magnitude and direction (humoral or cellular) of the **vaccine**-induced immune responses in rodent models. To date, however, there has been very little data reported from studies in primates. In this study, we examined the effects of cytokine gene adjuvants to enhance the level of cell-mediated immune responses in rhesus macaques. We co-immunized rhesus macaques with expression **plasmids** encoding for IL-2, IFN-gamma or IL-4 cytokines along with the **DNA vaccine** constructs encoding for **HIV** env/rev (pCEnv) and SIV gag/pol (pCSGag/pol) proteins. We observed that coadministration of IL-2 and IFN-gamma cDNA resulted in enhancement of antigen-specific T cell-mediated immune responses.

L54 ANSWER 51 OF 132 MEDLINE on STN

2001409101. PubMed ID: 11257382. Expansion of HBV-specific memory **CTL** primed by dual **HIV**/HBV **genetic** immunization during SHIV primary infection in rhesus macaques. Borgne S L; Michel M L; Camugli S; Corre B; Le Grand R; Riviere Y. (Departement des Retrovirus, Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, 28, rue du

(17-19) 2485-95. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB We have previously shown the induction of humoral and **cytotoxic** responses specific for **human immunodeficiency virus** (**HIV**) and hepatitis B virus (HBV) antigens, following **genetic** immunization of rhesus macaques with a **plasmid** encoding both the third variable domain of the **HIV**-1 external envelope glycoprotein and the pseudo-viral particle of hepatitis B surface antigen (HBsAg) as presenting molecules. The **DNA**-immunized primates and two control animals were then challenged with a chimeric simian/**human immunodeficiency virus** (SHIV). They were all infected. Significant frequencies of SHIV specific **cytotoxic** T lymphocyte precursors (CTLp) were detected early in peripheral blood. But, in all **DNA**-immunized macaques, HBV envelope specific CTLp were detected during the primary infection, and they were correlated with the peak of SHIV viremia. Furthermore, HBV or SHIV specific cytotoxicity corresponded in part to CD8(+) T cells presenting a memory phenotype. Several mechanisms could account for this cellular response. But our results suggest that an expansion of memory **cytotoxic** CD8(+) cells, not restricted to SHIV specific effectors, could occur in peripheral blood during SHIV primary infection.

L54 ANSWER 52 OF 132 MEDLINE on STN

2001408725. PubMed ID: 11228392. Induction of virus-specific **cytotoxic** T lymphocytes by in vivo electric administration of peptides. Uno-Furuta S; Tamaki S; Takebe Y; Takamura S; Kamei A; Kim G; Kuromatsu I; Kaito M; Adachi Y; Yasutomi Y. (Department of Bioregulation, Mie University School of Medicine, 2-174 Edobashi, Tsu 514-8507, Mie, Japan.) Vaccine, (2001 Feb 28) 19 (15-16) 2190-6. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Generally, major histocompatibility complex (MHC) **class I** presentation of peptide antigens only occur for proteins' which are actively synthesized and processed intracellularly, so that immunization with a **cytotoxic** T lymphocyte (**CTL**) target peptide does not usually elicit effective **CTL** responses. In the present study, we explored the use of epitope peptides by in vivo electroporation to introduce directly into the cytoplasm for the **vaccine** elicitation of virus-specific CTLs in a mouse system. BALB/c mice were immunized with **human immunodeficiency virus** (**HIV**) env (P18, residues 311-320) or hepatitis C virus (HCV) NS5 (P17, residues 2423-2434) with or without electric pulses. Effector cells against peptide-labeled target cells were elicited in mice immunized with peptides with electric administration but not without electric administration. Moreover, cytolytic activities of **CTL** against peptide-labeled target cells were enhanced by the addition of **plasmid** having the immunostimulatory sequence (ISS) or cDNA of the B7-1 molecule in electric administration of peptides. The results of the present study suggest that a peptide **vaccine** against a virus using electric administration is effective in eliciting virus specific CTLs.

L54 ANSWER 53 OF 132 MEDLINE on STN

2001408708. PubMed ID: 11228375. **DNA vaccination** in mice using **HIV**-1 nef, rev and tat genes in self-replicating pBN-vector. Tahtinen M; Strengell M; Collings A; Pitkanen J; Kjerrstrom A; Hakkarainen K; Peterson P; Kohleisen B; Wahren B; Ranki A; Ustav M; Krohn K. (Institute of Medical Technology, Tampere University, 33014, Tampere, Finland.. mtahtine@csc.fi) . Vaccine, (2001 Feb 28) 19 (15-16) 2039-47. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB The immunogenicity of a self-replicating **DNA**-vector containing **HIV**-1 nef gene (pBN-Nef) was characterized using various **DNA** delivery methods. In addition, gene gun immunisation was used for assessing immunogenicity of two other **HIV**-1 genes (rev and tat) given in the same vector. The pBN-Nef was the most immunogenic raising both humoral and cell-mediated immune responses in mice; these responses lasted for up to six months. The pBN-Nef vector was immunogenic also when given intramuscularly or intradermally. The pBN-Rev construct did not elicit humoral responses but did elicit proliferative as well as **CTL**-response against the

corresponding protein. The p27 Tat was a poor immunogen in all responses. The antibodies elicited with various **DNA** delivery methods belonged to different antibody subclasses; however, two main epitopes in Nef were frequently recognized by all of them.

L54 ANSWER 54 OF 132 MEDLINE on STN
2001355199. PubMed ID: 11282211. Enhancement of mucosal immune response against **HIV**-1 Gag by **DNA** immunization. Yoshizawa I; Soda Y; Mizuochi T; Yasuda S; Rizvi T A; Mizuochi T; Takemori T; Tsunetsugu-Yokota Y. (Department of Immunology, National Institute of Infectious Diseases, 1-23-1 Toyama-cho, Shinjuku-ku, Tokyo 162-8640, Japan.) Vaccine, (2001 Apr 6) 19 (20-22) 2995-3003. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB In order to examine the feasibility of Gag-expression **DNA** as a potential candidate for **HIV vaccine** using a mouse model, we injected **DNA** into mice either intramuscularly or by using a gene gun. Both methods induced a low level of antibody production. However, after booster immunization with p24 protein emulsified with complete Freund's adjuvant via a footpad, we found that only the preceding intramuscular **DNA** immunization induced an anti-Gag Th1-type (IgG(2a)) antibody response, in addition to the enhancement of a Th2-type (IgG(1)) antibody response. Importantly, when mice were boosted intranasally with p24 and cholera toxin, intramuscular **DNA injection** was found to enhance both systemic and mucosal Gag-specific immune responses. These results indicate that intramuscular **DNA** immunization confers the inducibility of memory cells, which circulate around various mucosal tissues. Therefore, intramuscular **DNA** priming, followed by a mucosal booster immunization, could be considered as a regimen applicable to **HIV vaccine**.

L54 ANSWER 55 OF 132 MEDLINE on STN
2001355181. PubMed ID: 11282190. Modulation of cellular and humoral immune responses to a multiepitopic **HIV**-1 **DNA vaccine** by interleukin-18 **DNA** immunization/viral protein boost. Billaut-Mulot O; Idziorek T; Loyens M; Capron A; Bahr G M. (Laboratory of Molecular Immunology of Infection and Inflammation, Institut Pasteur de Lille, 1 rue du Pr Calmette, BP 245, 59019 Lille Cedex, France.) Vaccine, (2001 Apr 6) 19 (20-22) 2803-11. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB In this study, the impact of Th1-inducing cytokine gene co-delivery and antigen boosting on humoral and cellular responses induced by multiepitopic **DNA** immunization in mice have been investigated. Intramuscular injection of mixed **DNA** constructs encoding for **HIV**-1 Gag, Tat and Nef proteins, co-administered with the **DNA** encoding for interleukin-18 (IL-18) have been used. The effect of boosting with the recombinant proteins was also evaluated on the outcome of the responses in **DNA**-primed mice. It was demonstrated that at least two **DNA** immunizations were necessary to generate virus specific Th-1 responses detected by the presence of **cytotoxic** T lymphocyte (**CTL**) and by the secretion of IL-2 and IFN-gamma, but not IL-4 and IL-10, in antigen-stimulated splenocyte cultures. Interestingly, co-delivery of Th-1-inducing IL-18 gene was able to shorten by 2 weeks, the **CTL** induction time, and to increase the antigen-induced secretion of IL-2 and IFN-gamma. Furthermore, IL-18 co-delivery enhanced antigen-specific lymphoproliferative responses, and this was most evident in mice that were primed and boosted with **plasmid DNA**. However, the induction of detectable antibodies in mice required two **DNA vaccinations** and a protein boost. In contrast to the effects on cell-mediated immunity, co-administration of IL-18-**plasmid** resulted in decreased antibody titers against viral proteins.

L54 ANSWER 56 OF 132 MEDLINE on STN
2001201552. PubMed ID: 11153083. Construction, biological activity, and immunogenicity of synthetic envelope **DNA vaccines** based on a primary, CCR5-tropic, early **HIV** type 1 isolate (BX08) with human codons. Corbet S; Vinner L; Hougaard D M; Bryder K; Nielsen H V; Nielsen C; Fomsgaard A. (Department of Virology Statens Serum Institute, DK-2300 Copenhagen,

1997-2008. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB So far codon-optimized **HIV**-1 envelope genes have been investigated for the T cell line-adapted strain MN, which differs in several aspects from primary isolates. Envelopes of primary isolates may be more relevant for **vaccine** purposes. This article describes for the first time the engineering and characterization of four "humanized" genes encoding the secreted gp120/gp140, or the membrane-bound gp150/gp160, of a primary CCR5 tropic, clade B, clinical isolate **HIV**-1(BX08). The genes were built in fragments for easy cassette exchange of regions important for immunogenicity, function, and expression. The transcription and expression of the synthetic genes in mammalian cell lines were Rev independent and highly increased. Increased expression of membrane-bound gp160 induced a high cytopathic effect in U87.CD4.CCR5 cells. Gene gun and intramuscular **DNA vaccination** in mice induced a strong specific **cytotoxic** T lymphocyte response independent of the gene construct, expression level, or **DNA** immunization route. In contrast, the highest anti-gp120 antibody levels were induced by synthetic genes encoding the secreted glycoproteins followed by gp160/gp150. Unlike **HIV**-1(MN), **HIV**-1(BX08) V3 was not immune dominant. Despite the high antibody response only low and inconsistent neutralizing titers to the homologous **HIV**-1 isolate were measured. However, neutralization of SHIV89.6P could be obtained. Thus, the neutralizing epitopes on the cell line-adapted SHIV89.6P and **HIV**-1(MN) may be more antigenically available for the cross-neutralizing antibodies induced. In conclusion, complete "humanization" of the **DNA vaccine** genes failed to induce a consistent neutralizing antibody response, albeit expression and immunogenicity of the primary **HIV**-1 glycoproteins were greatly improved. Optimization in terms of improving neutralization may require further modifications of the **DNA vaccine** gene. The synthetic cassette construct described is a convenient tool developed to investigate this further.

L54 ANSWER 57 OF 132 MEDLINE on STN

2001180944. PubMed ID: 11160750. Elicitation of high-frequency **cytotoxic** T-lymphocyte responses against both dominant and subdominant simian-**human immunodeficiency virus** epitopes by **DNA vaccination** of rhesus monkeys. Barouch D H; Craiu A; Santra S; Egan M A; Schmitz J E; Kuroda M J; Fu T M; Nam J H; Wyatt L S; Lifton M A; Krivulka G R; Nickerson C E; Lord C I; Moss B; Lewis M G; Hirsch V M; Shiver J W; Letvin N L. (Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. dan_barouch@hotmail.com) . Journal of virology, (2001 Mar) 75 (5) 2462-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Increasing evidence suggests that the generation of **cytotoxic** T-lymphocyte (**CTL**) responses specific for a diversity of viral epitopes will be needed for an effective **human immunodeficiency virus** type 1 (**HIV**-1) **vaccine**. Here, we determine the frequencies of **CTL** responses specific for the simian immunodeficiency virus Gag p11C and **HIV**-1 Env p41A epitopes in simian-**human immunodeficiency virus** (SHIV)-infected and **vaccinated** rhesus monkeys. The p11C-specific **CTL** response was high frequency and dominant and the p41A-specific **CTL** response was low frequency and subdominant in both SHIV-infected monkeys and in monkeys **vaccinated** with recombinant modified **vaccinia** virus Ankara vectors expressing these viral antigens. Interestingly, we found that **plasmid DNA vaccination** led to high-frequency **CTL** responses specific for both of these epitopes. These data demonstrate that **plasmid DNA** may be useful in eliciting a broad **CTL** response against multiple epitopes.

L54 ANSWER 58 OF 132 MEDLINE on STN

2001171404. PubMed ID: 11168828. Immune responses following simian/**human immunodeficiency virus** (SHIV) challenge of rhesus macaques after **human immunodeficiency virus** (**HIV**)-1 third variable domain (V3) loop-based **genetic** immunization. Le Borgne S; Le Grand R; Michel M L; Vaslin B; Boson B; Janvier G; Aubertin A M; Dormont D; Riviere Y.

(Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, Paris, France.. riviere@pasteur.fr) . Journal of medical primatology, (2000 Dec) 29 (6) 371-86. Journal code: 0320626. ISSN: 0047-2565. Pub. country: Denmark. Language: English.

AB Following **DNA** immunization of rhesus macaques with a **plasmid** encoding the **human immunodeficiency virus** (**HIV**)-1 third variable domain (V3) loop, presented by pseudo-viral envelope particles of hepatitis B virus, specific immune responses were induced. The primates were then inoculated with a chimeric simian/**human immunodeficiency virus** (SHIV). All the animals were infected, but the V3-specific immunization provided a relative attenuation of the acute phase of infection in the absence of neutralizing antibody. In all animals, SHIV-specific **cytotoxic** T-lymphocyte precursors (CTLp) were detected early in peripheral blood and lymph nodes. The viremia peak correlated significantly with the decrease in CD4+ T cells and with a transient increase in the percentage of natural killer cells. The infection induced an oligoclonalization of the CD8+ T-cell variable beta chain repertoire in the blood. Surprisingly, **HIV** envelope-specific CTLp generated by **genetic** immunization may be governed by distinct circulation rules compared to SHIV-specific CTLp induced by infection.

L54 ANSWER 59 OF 132 MEDLINE on STN

2001133497. PubMed ID: 11145897. **DNA vaccination** of macaques with several different Nef sequences induces multispecific T cell responses. Couillin I; Letourneur F; Lefebvre P; Guillet J G; Martinon F. (Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France.) Virology, (2001 Jan 5) 279 (1) 136-45. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary **human immunodeficiency virus**-1 and in maintaining disease-free infection. It has recently been shown that **DNA** immunization of rhesus monkeys can elicit strong, long-lived antigen-specific **cytotoxic** T lymphocyte (**CTL**) responses. In previous work, it was shown that macaque **CTL** responses to lipopeptide **vaccination** were directed against a limited number of epitopes. In the present study, we used the **DNA** immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six **plasmids** reflecting the variability of Nef epitopic regions in the simian immunodeficiency virus (SIV) mac251 primary isolate. The Nef genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that **DNA** immunization with Nef sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of Nef. Reacting T cell lines were expanded in vitro and multispecific **CTL** responses mapping the 96-138 Nef region were analyzed. Several peptides recognized by **CTL** were identified and studies using peptides reflecting the variability of Nef indicated that all of the Nef variants were recognized in the 96-138 region. Moreover, **CTL** responses were directed against an immunodominant epitope located in a functional region within the Nef protein that is essential for viral replication. This work shows that our approach of **DNA** immunization with several sequences induced multispecific T cell responses recognizing variants included in the SIVmac251 primary isolate.

L54 ANSWER 60 OF 132 MEDLINE on STN

2001091115. PubMed ID: 11120800. Functional equivalency of B7-1 and B7-2 for costimulating **plasmid DNA vaccine**-elicited **CTL** responses. Santra S; Barouch D H; Jackson S S; Kuroda M J; Schmitz J E; Lifton M A; Sharpe A H; Letvin N L. (Department of Medicine, Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.) Journal of immunology (Baltimore, Md. : 1950), (2000 Dec 15) 165 (12) 6791-5. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB A costimulatory signal in addition to an Ag-specific stimulus is required for optimal activation of T lymphocytes. CD28, the primary positive costimulatory receptor on T cells, has two identified ligands, B7-1 and B7-2. Whether B7-1 and B7-2 have identical, overlapping, or distinct functions remains unresolved. In this study, we show that mice lacking B7-2 were unable to generate **CTL** responses following immunization with a **plasmid DNA vaccine**. The ability of these B7-2-deficient mice to generate **CTL** responses following **plasmid** gp120 **DNA vaccination** was fully reconstituted by coadministering either a **plasmid** expressing B7-2 or B7-1. Moreover, the ability to generate **CTL** responses following **plasmid DNA vaccination** in mice lacking both B7-1 and B7-2 could be reconstituted by administering either **plasmid** B7-1 or **plasmid** B7-2 with the **vaccine** construct. These data demonstrate that either B7-1 or B7-2 administered concurrently with a **plasmid DNA vaccine** can fully costimulate **vaccine**-elicited **CTL** responses. Functional differences between B7-1 and B7-2 observed in vivo therefore may not reflect inherent differences in the interactions of CD28 with these ligands.

L54 ANSWER 61 OF 132 MEDLINE on STN
2001083019. PubMed ID: 11090158. Enhancing B- and T-cell immune response to a hepatitis C virus E2 **DNA vaccine** by intramuscular electrical gene transfer. Zucchelli S; Capone S; Fattori E; Folgori A; Di Marco A; Casimiro D; Simon A J; Laufer R; La Monica N; Cortese R; Nicosia A. (Istituto di Ricerche di Biologia Molecolare P. Angeletti, 00040 Pomezia (Rome), Italy.) Journal of virology, (2000 Dec) 74 (24) 11598-607. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We describe an improved **genetic** immunization strategy for eliciting a full spectrum of anti-hepatitis C virus (HCV) envelope 2 (E2) glycoprotein responses in mammals through electrical gene transfer (EGT) of **plasmid DNA** into muscle fibers. Intramuscular injection of a **plasmid** encoding a cross-reactive hypervariable region 1 (HVR1) peptide mimic fused at the N terminus of the E2 ectodomain, followed by electrical stimulation treatment in the form of high-frequency, low-voltage electric pulses, induced more than 10-fold-higher expression levels in the transfected mouse tissue. As a result of this substantial increment of in vivo antigen production, the humoral response induced in mice, rats, and rabbits ranged from 10- to 30-fold higher than that induced by conventional **naked DNA** immunization. Consequently, immune sera from EGT-treated mice displayed a broader cross-reactivity against HVR1 variants from natural isolates than sera from injected animals that were not subjected to electrical stimulation. Cellular response against E2 epitopes specific for helper and **cytotoxic** T cells was significantly improved by EGT. The EGT-mediated enhancement of humoral and cellular immunity is antigen independent, since comparable increases in antibody response against ciliary neurotrophic factor or in specific anti-**human immunodeficiency virus** type 1 gag CD8(+) T cells were obtained in rats and mice. Thus, the method described potentially provides a safe, low-cost treatment that may be scaled up to humans and may hold the key for future development of prophylactic or therapeutic **vaccines** against HCV and other infectious diseases.

L54 ANSWER 62 OF 132 MEDLINE on STN
2001010079. PubMed ID: 10973449. Interleukin 7 can enhance antigen-specific **cytotoxic**-T-lymphocyte and/or Th2-type immune responses in vivo. Sin J I; Kim J; Pachuk C; Weiner D B; Patchuk C. (Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.) Clinical and diagnostic laboratory immunology, (2000 Sep) 7 (5) 751-8. Journal code: 9421292. ISSN: 1071-412X. Pub. country: United States. Language: English.

AB Interleukin 7 (IL-7) protein has been reported to be important in the development of **cytotoxic**-T-lymphocyte (**CTL**) responses. However, other studies also support a partial Th2 phenotype for this cytokine. In an effort to clarify this unusual conflict, we compared IL-7 along with IL-12 (Th1 control) and IL-10 (Th2 control) for its ability to induce antigen (Ag)-specific **CTL** and Th1- versus Th2-type immune responses using a well

a significant increase in immunoglobulin G1 (IgG1) levels compared to IgG2a levels. IL-7 coinjection also decreased production of Th1-type cytokine IL-2, gamma interferon, and the chemokine RANTES but increased production of the Th2-type cytokine IL-10 and the similarly biased chemokine MCP-1. In herpes simplex virus (HSV) challenge studies, IL-7 coinjection decreased the survival rate after lethal HSV type 2 (HSV-2) challenge compared with gD **plasmid vaccine** alone in a manner similar to IL-10 coinjection, whereas IL-12 coinjection enhanced the protection, further supporting that IL-7 drives immune responses to the Th2 type, resulting in reduced protection against HSV-2 challenge. Moreover, coinjection with **human immunodeficiency virus** type 1 env and gag/pol genes plus IL-12 or IL-7 cDNA enhanced Ag-specific CTLs, while coinjection with IL-10 cDNA failed to influence **CTL** induction. Thus, IL-7 could drive Ag-specific Th2-type cellular responses and/or **CTL** responses. These results support that CTLs could be induced by IL-7 in a Th2-type cytokine and chemokine environment in vivo. This property of IL-7 allows for an alternative pathway for **CTL** development which has important implications for host-pathogen responses.

L54 ANSWER 63 OF 132 MEDLINE on STN
2000490347. PubMed ID: 11039923. Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented **DNA vaccination**. Barouch D H; Santra S; Schmitz J E; Kuroda M J; Fu T M; Wagner W; Bilska M; Craiu A; Zheng X X; Krivulka G R; Beaudry K; Lifton M A; Nickerson C E; Trigona W L; Punt K; Freed D C; Guan L; Dubey S; Casimiro D; Simon A; Davies M E; Chastain M; Strom T B; Gelman R S; Montefiori D C; Lewis M G; Emini E A; Shiver J W; Letvin N L. (Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA.. dan_barouch@hotmail.com) . Science, (2000 Oct 20) 290 (5491) 486-92. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB With accumulating evidence indicating the importance of **cytotoxic** T lymphocytes (CTLs) in containing **human immunodeficiency virus**-1 (**HIV**-1) replication in infected individuals, strategies are being pursued to elicit virus-specific CTLs with prototype **HIV**-1 **vaccines**. Here, we report the protective efficacy of **vaccine**-elicited immune responses against a pathogenic SHIV-89.6P challenge in rhesus monkeys. Immune responses were elicited by **DNA vaccines** expressing SIVmac239 Gag and **HIV**-1 89.6P Env, augmented by the administration of the purified fusion protein IL-2/Ig, consisting of interleukin-2 (IL-2) and the Fc portion of immunoglobulin G (IgG), or a **plasmid** encoding IL-2/Ig. After SHIV-89.6P infection, sham-**vaccinated** monkeys developed weak **CTL** responses, rapid loss of CD4+ T cells, no virus-specific CD4+ T cell responses, high setpoint viral loads, significant clinical disease progression, and death in half of the animals by day 140 after challenge. In contrast, all monkeys that received the **DNA vaccines** augmented with IL-2/Ig were infected, but demonstrated potent secondary **CTL** responses, stable CD4+ T cell counts, preserved virus-specific CD4+ T cell responses, low to undetectable setpoint viral loads, and no evidence of clinical disease or mortality by day 140 after challenge.

L54 ANSWER 64 OF 132 MEDLINE on STN
2000465940. PubMed ID: 11017793. **DNA vaccination** of macaques by a full genome **HIV**-1 **plasmid** which produces noninfectious virus particles. Akahata W; Ido E; Shimada T; Katsuyama K; Yamamoto H; Uesaka H; Ui M; Kuwata T; Takahashi H; Hayami M. (Laboratory of Viral Pathogenesis, Institute for Virus Research, Kyoto 606-8507, Japan.) Virology, (2000 Sep 15) 275 (1) 116-24. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB In this study, we tried a **DNA vaccination** regime in rhesus macaques using a full genome **HIV**-1 **plasmid**. The **HIV**-1 genome is under the control of its original LTR promoter, but has a mutated zinc finger motif gene in the nucleocapsid region. Due to the lack of genomic RNA packaging, the **plasmid** produces only noninfectious viral particles. We repeatedly injected four macaque monkeys intramuscularly with the **naked**

DNA over a period of 48 weeks. To evaluate the humoral and cell-mediated immunity provided by this **DNA vaccination**, no other booster or other recombinant viral vectors were used. Immunological responses against **HIV**-1 were elicited in all of the **vaccinated** monkeys: stable anti-**HIV**-1 Env antibodies were raised in two monkeys and **CTL** activities were induced in the other monkeys. The macaques were intravenously challenged at 54 weeks with 100 TCID(50) of SHIV-NM-3rN, which possesses an envelope gene homologous to the one in the **vaccinated plasmid**. In all of the **vaccinated** macaques, the peak plasma viral loads induced by the challenge virus were two to three orders of magnitude lower than those of the naive controls. These results suggest that a **DNA vaccination** regime with a full genome **plasmid** alone is potentially efficacious and provides a new possibility for the development of an AIDS **vaccine**.

L54 ANSWER 65 OF 132 MEDLINE on STN
2000454646. PubMed ID: 10967024. Creating **HIV**-1 reverse transcriptase **cytotoxic** T lymphocyte target structures by HLA-A2 heavy chain modifications. Dela Cruz C S; Tan R; Rowland-Jones S L; Barber B H. (Department of Immunology and Institute of Medical Science, University of Toronto, Medical Sciences Building, 1 King's College Circle, Ontario M5S 1A8, Canada.) International immunology, (2000 Sep) 12 (9) 1293-302. Journal code: 8916182. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vigorous **HIV**-1-specific CD8(+) **cytotoxic** T lymphocyte (**CTL**) responses play an important role in the control of **HIV**-1 replication and the induction of a strong, broadly cross-reactive **CTL** response remains an important goal of **HIV vaccine** development. It is known that the display of high levels of **class I** MHC-viral peptide complexes at the cell surface of target cells is necessary to elicit a strong **CTL** response. We now report two strategies to enhance the presentation of defined **HIV**-1 epitope-specific **CTL** target structures, by incorporating subdominant **HIV**-1 reverse transcriptase (RT) **CTL** epitope sequences into the human **class I** MHC molecule HLA-A2. We show that either incorporation of **HIV**-1 **CTL** epitopes into the signal sequence of HLA or tethering of epitopes to the HLA-A2 heavy chain provide simple ways to create effective **CTL** target structures that can be recognized and lysed by human HLA-A2-restricted RT-specific CD8(+) **CTL**. Moreover, cells expressing these epitope-containing HLA-A2 constructs stimulated the generation of primary epitope-specific **CTL** in vitro. These strategies offer new options in the design of **plasmid DNA-based vaccines** or immunotherapeutics for the induction of **CTL** responses against subdominant **HIV**-1 epitopes.

L54 ANSWER 66 OF 132 MEDLINE on STN
2000452718. PubMed ID: 11009099. B7 co-stimulatory requirements differ for induction of immune responses by **DNA**, protein and recombinant pox virus **vaccination**. Santra S; Barouch D H; Sharpe A H; Letvin N L. (Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.) European journal of immunology, (2000 Sep) 30 (9) 2650-9. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Whether B7-1 and B7-2 have distinct functions for eliciting immune responses to antigens that are presented to the immune system by intracellular and extracellular antigen processing pathways is an unresolved question. To investigate this issue we compared the humoral and cellular immune responses elicited by immunizing wild-type, B7-1-/- and B7-2-/- mice with either **HIV**-1 gp120 **plasmid DNA**, recombinant gp120 protein or **vaccinia** virus expressing gp120. The generation of both humoral and cellular immune responses to an antigen produced intracellularly following **DNA vaccination** had critical requirements for B7-2, but not B7-1. Neither of the molecules was essential for the generation of antibody responses to an extracellular protein antigen administered with adjuvant; B7-1 had little effect on the elicited immune responses. When recombinant **vaccinia** virus was used to present antigen

required for antibody and T cell proliferative responses, but it exerted a suppressive effect on the elicited **CTL** activity. These results demonstrate that antigens presented to the immune system by different mechanisms have distinct B7-1 and B7-2 co-stimulatory requirements.

L54 ANSWER 67 OF 132 MEDLINE on STN
2000427428. PubMed ID: 10940883. Conjugation of protein to immunostimulatory **DNA** results in a rapid, long-lasting and potent induction of cell-mediated and humoral immunity. Tighe H; Takabayashi K; Schwartz D; Marsden R; Beck L; Corbeil J; Richman D D; Eiden J J Jr; Spiegelberg H L; Raz E. (Department of Medicine, The Sam and Rose Stein Institute for Research of Aging, University of California, San Diego, La Jolla 92093-0663, USA.. htighe@ucsd.edu) . European journal of immunology, (2000 Jul) 30 (7) 1939-47. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Immunostimulatory **DNA** sequences (ISS) are a potent Th1 adjuvant. We hypothesized that conjugation of ISS to protein antigens would strongly enhance their immunogenicity because both antigen and adjuvant (ISS) would be delivered to the same locale/antigen-presenting cell. To test this hypothesis, we conjugated a 22-mer immunostimulatory oligodeoxynucleotide (ISS-ODN) to two test antigens of differing intrinsic immunogenicity, namely Escherichia coli beta-galactosidase and the **HIV**-1 envelope glycoprotein gp120. We show that the antigen-ISS conjugates rapidly induce Th1 cells secreting high levels of IFN-gamma, strong **CTL** activity, and high titer IgG2a and **HIV**-neutralizing antibodies, exceeding gene and protein **vaccination** alone or immunization with mixtures of antigen and ISS-ODN. The data suggest that this procedure generates a novel and unique **vaccine** that rapidly triggers strong humoral and cell-mediated immunity.

L54 ANSWER 68 OF 132 MEDLINE on STN
2000407911. PubMed ID: 10856795. Anti-major histocompatibility complex antibody responses in macaques via intradermal **DNA** immunizations. Dela Cruz C S; MacDonald K S; Barber B H. (Institute of Medical Sciences, Medical Sciences Building, University of Toronto, 1 King's College Circle, Ontario, M5S 1A8, Toronto, Canada.) Vaccine, (2000 Jul 15) 18 (27) 3152-65. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB In simian immunodeficiency virus (SIV) models, immunization of macaques with uninfected human cells or human major histocompatibility complex (MHC) proteins can induce xenogeneic immune responses which can protect the animals from subsequent SIV challenges. These studies suggest that the induction of anti-MHC immune responses can be a viable **vaccine** strategy against **human immunodeficiency virus** type 1 (**HIV**-1). We have previously shown in mouse studies that **DNA** immunization with **class I** and class II MHC-encoding **plasmids** can elicit both xenogeneic and allogeneic antibody responses against conformationally intact MHC molecules (**Vaccine** 17 (1999) 2479-92). Here we take these observations one step closer to human applications and report that intradermal needle immunizations of non-human primates with **plasmid DNA** encoding human MHC alleles can safely elicit xenogeneic anti-MHC antibody responses. Moreover, injecting macaques with **DNA** encoding a specific macaque allogeneic MHC induced anti-allogeneic MHC antibodies production. These studies show that **DNA** immunization with MHC-encoding vectors can indeed be used to induce specific anti-human xenogeneic, as well as anti-macaque allogeneic MHC immunity in non-human primates. This strategy could thus be used to mobilize anti-MHC antibody response which may be useful as part of an anti-**HIV**-1 **vaccination** approach.

L54 ANSWER 69 OF 132 MEDLINE on STN
2000405861. PubMed ID: 10906202. Simian immunodeficiency virus (SIV) gag **DNA-vaccinated** rhesus monkeys develop secondary **cytotoxic** T-lymphocyte responses and control viral replication after pathogenic SIV infection. Egan M A; Charini W A; Kuroda M J; Schmitz J E; Racz P; Tenner-Racz K; Manson K; Wyand M; Lifton M A; Nickerson C E; Fu T; Shiver

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. eganm@WAR.Wyeth.com) . Journal of virology, (2000 Aug) 74 (16) 7485-95. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The potential contribution of a **plasmid DNA** construct to **vaccine**-elicited protective immunity was explored in the simian immunodeficiency virus (SIV)/macaque model of AIDS. Making use of soluble major histocompatibility **class I**/peptide tetramers and peptide-specific killing assays to monitor CD8(+) T-lymphocyte responses to a dominant SIV Gag epitope in genetically selected rhesus monkeys, a codon-optimized SIV gag **DNA vaccine** construct was shown to elicit a high-frequency SIV-specific **cytotoxic** T-lymphocyte (**CTL**) response. This **CTL** response was demonstrable in both peripheral blood and lymph node lymphocytes. Following an intravenous challenge with the highly pathogenic viral isolate SIVsm E660, these **vaccinated** monkeys developed a secondary **CTL** response that arose with more rapid kinetics and reached a higher frequency than did the postchallenge **CTL** response in control **plasmid-vaccinated** monkeys. While peak plasma SIV RNA levels were comparable in the experimentally and control-**vaccinated** monkeys during the period of primary infection, the gag **plasmid DNA-vaccinated** monkeys demonstrated better containment of viral replication by 50 days following SIV challenge. These findings indicate that a **plasmid DNA vaccine** can elicit SIV-specific **CTL** responses in rhesus monkeys, and this **vaccine**-elicited immunity can facilitate the generation of secondary **CTL** responses and control of viral replication following a pathogenic SIV challenge. These observations suggest that **plasmid DNA** may prove a useful component of a **human immunodeficiency virus** type 1 **vaccine**.

L54 ANSWER 70 OF 132 MEDLINE on STN

2000226080. PubMed ID: 10759543. Augmentation of immune responses to **HIV**-1 and simian immunodeficiency virus **DNA vaccines** by IL-2/Ig **plasmid** administration in rhesus monkeys. Barouch D H; Craiu A; Kuroda M J; Schmitz J E; Zheng X X; Santra S; Frost J D; Krivulka G R; Lifton M A; Crabbs C L; Heidecker G; Perry H C; Davies M E; Xie H; Nickerson C E; Steenbeke T D; Lord C I; Montefiori D C; Strom T B; Shiver J W; Lewis M G; Letvin N L. (Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2000 Apr 11) 97 (8) 4192-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The potential utility of **plasmid DNA** as an **HIV**-1 **vaccination** modality currently is an area of active investigation. However, recent studies have raised doubts as to whether **plasmid DNA** alone will elicit immune responses of sufficient magnitude to protect against pathogenic AIDS virus challenges. We therefore investigated whether **DNA vaccine**-elicited immune responses in rhesus monkeys could be augmented by using either an IL-2/Ig fusion protein or a **plasmid** expressing IL-2/Ig. Sixteen monkeys, divided into four experimental groups, were immunized with (i) sham **plasmid**, (ii) **HIV**-1 Env 89.6P and simian immunodeficiency virus mac239 Gag **DNA vaccines** alone, (iii) these **DNA vaccines** and IL-2/Ig protein, or (iv) these **DNA vaccines** and IL-2/Ig **plasmid**. The administration of both IL-2/Ig protein and IL-2/Ig **plasmid** induced a significant and sustained in vivo activation of peripheral T cells in the **vaccinated** monkeys. The monkeys that received IL-2/Ig **plasmid** generated 30-fold higher Env-specific antibody titers and 5-fold higher Gag-specific, tetramer-positive CD8+ T cell levels than the monkeys receiving the **DNA vaccines** alone. IL-2/Ig protein also augmented the **vaccine**-elicited immune responses, but less effectively than IL-2/Ig **plasmid**. Augmentation of the immune responses by IL-2/Ig was evident after the primary immunization and increased with subsequent boost immunizations. These results demonstrate that the administration of IL-2/Ig **plasmid** can substantially augment **vaccine**-elicited humoral and cellular immune responses in higher primates.

L54 ANSWER 71 OF 132 MEDLINE on STN
2000184009. PubMed ID: 10717340. Targeted expression of HTLV-I envelope proteins in muscle by **DNA** immunization of mice. Armand M A; Grange M P; Paulin D; Desgranges C. (Virus des hepatites, retrovirus humains et pathologies associees, INSERM U271, Lyon, France.) Vaccine, (2000 Apr 28) 18 (21) 2212-22. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have compared two types of **plasmids** for **DNA** immunization against HTLV-I envelope glycoproteins. One type of **plasmid** contains the coding **DNA** of the complete envelope gene of HTLV-I under the control of the CMV promoter with (CMVenvLTR) or without (CMVenv) the tax/rex genes. The second type contains the coding **DNA** of the complete env gene of HTLV-I under the control of the human desmin muscle specific promoter (DesEnv). These **plasmids** were inoculated into mice and the humoral response was studied by flow cytometry, ELISA and neutralization assays. Inoculation of the DesEnv construct elicited a higher humoral response with better neutralization properties than the injection of CMVenvLTR or CMVenv **plasmids**. The choice of vectors will be important for the design of **genetic** HTLV-I **vaccines**.

L54 ANSWER 72 OF 132 MEDLINE on STN
2000148954. PubMed ID: 10684277. Increased expression and immunogenicity of sequence-modified **human immunodeficiency virus** type 1 gag gene. zur Megede J; Chen M C; Doe B; Schaefer M; Greer C E; Selby M; Otten G R; Barnett S W. (Chiron Corporation, Emeryville, California 94608, USA.) Journal of virology, (2000 Mar) 74 (6) 2628-35. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A major challenge for the next generation of **human immunodeficiency virus (HIV) vaccines** is the induction of potent, broad, and durable cellular immune responses. The structural protein Gag is highly conserved among the **HIV** type 1 (**HIV**-1) gene products and is believed to be an important target for the host cell-mediated immune control of the virus during natural infection. Expression of Gag proteins for **vaccines** has been hampered by the fact that its expression is dependent on the **HIV** Rev protein and the Rev-responsive element, the latter located on the env transcript. Moreover, the **HIV** genome employs suboptimal codon usage, which further contributes to the low expression efficiency of viral proteins. In order to achieve high-level Rev-independent expression of the Gag protein, the sequences encoding **HIV**-1(SF2) p55(Gag) were modified extensively. First, the viral codons were changed to conform to the codon usage of highly expressed human genes, and second, the residual inhibitory sequences were removed. The resulting modified gag gene showed increases in p55(Gag) protein expression to levels that ranged from 322- to 966-fold greater than that for the native gene after transient expression of 293 cells. Additional constructs that contained the modified gag in combination with modified protease coding sequences were made, and these showed high-level Rev-independent expression of p55(Gag) and its cleavage products. Density gradient analysis and electron microscopy further demonstrated that the modified gag and gag protease genes efficiently expressed particles with the density and morphology expected for **HIV** virus-like particles. Mice immunized with **DNA plasmids** containing the modified gag showed Gag-specific antibody and CD8(+) **cytotoxic** T-lymphocyte (**CTL**) responses that were inducible at doses of input **DNA** 100-fold lower than those associated with **plasmids** containing the native gag gene. Most importantly, four of four rhesus monkeys that received two or three immunizations with modified gag **plasmid DNA** demonstrated substantial Gag-specific **CTL** responses. These results highlight the useful application of modified gag expression cassettes for increasing the potency of **DNA** and other gene delivery **vaccine** approaches against **HIV**.

L54 ANSWER 73 OF 132 MEDLINE on STN
2000143037. PubMed ID: 10680844. Macrophage colony-stimulating factor can modulate immune responses and attract dendritic cells in vivo. Kim J J; Yang J S; Lee D J; Wilson D M; Nottingham L K; Morrison L; Tsai A; Oh J; Dang K; Dentchev T; Agadjanyan M G; Sin J I; Chalian A A; Weiner D B.

(Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Human gene therapy, (2000 Jan 20) 11 (2) 305-21. Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English.

AB Studies have indicated that professional APCs in the periphery, such as dendritic cells and macrophages, play an important role in initiating **DNA vaccine**-specific immune responses. To engineer the immune response induced by **DNA vaccines** in vivo we investigated the modulatory effects of codelivering growth factor genes for the hematopoietic APCs along with **DNA vaccines**. Specifically, we examined the effects on the antigen-specific immune responses following the codelivery of the gene expression cassettes for M-CSF, G-CSF, and GM-CSF along with **HIV**-1 **DNA** immunogen constructs. We observed that coimmunization with GM-CSF increased the antibody response and resulted in a significant enhancement of lymphoproliferative response. Furthermore, among all coinjection combinations, we found that M-CSF coinjections resulted in a high level of **CTL** enhancement. This enhancement of **CTL** responses observed from the coinjection with M-CSF was CD8+ T cell dependent and was associated with the presence of CD11c+ cells at the site of injection and with the antigen-specific induction of the beta-chemokine MIP-1beta, suggesting a role for this chemokine in **CTL** induction. These results suggest that hematopoietic growth factors should be further studied as potential adjuvants for in vivo modulators of immune responses.

L54 ANSWER 74 OF 132 MEDLINE on STN

2000115963. PubMed ID: 10648178. Oral **DNA vaccination** promotes mucosal and systemic immune responses to **HIV** envelope glycoprotein. Kaneko H; Bednarek I; Wierzbicki A; Kiszka I; Dmochowski M; Wasik T J; Kaneko Y; Kozbor D. (Department of Microbiology, Thomas Jefferson University, 1020 Locust Street, Philadelphia, Pennsylvania, 19107-6799, USA.) Virology, (2000 Feb 1) 267 (1) 8-16. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB In this report, we described induction of **HIV** envelope (env)-specific systemic and mucosal immune responses by oral **vaccination** of BALB/c mice with env-encoded **plasmid DNA** encapsulated in poly(dl-lactide-co-glycolide) (PLG) microparticles. We demonstrated that intragastric administration of the encapsulated **plasmid DNA** resulted in transduced expression of the env glycoprotein in the intestinal epithelium. Mice immunized orally exhibited env-specific type 1 and **cytotoxic** T lymphocyte (**CTL**) responses in spleen and the inductive (Peyer's patches) and effector (lamina propria) mucosal tissues of gut. Oral administration of PLG-encapsulated **plasmid DNA** encoding gp160 also induced env-specific serum antibodies, and an increased level of IgA directed to gp160 was detected in fecal washes of the immunized mice. In contrast, intramuscular (i.m.) administration of **naked** or PLG-encapsulated **DNA vaccine** induced only systemic cellular and humoral responses to the env glycoprotein. Using an **HIV** env-expressing recombinant **vaccinia** viral intrarectal murine challenge system, we observed higher resistance to mucosal viral transmission in mice immunized orally than in animals injected i.m. with PLG-encapsulated **plasmid DNA** encoding gp160. Results of these studies demonstrate the feasibility of using orally delivered PLG microparticles containing **plasmid DNA**-encoded **HIV** gp160 for induction of env-specific systemic and mucosal immune responses and protection against recombinant **HIV** env **vaccinia** virus challenge. Copyright 2000 Academic Press.

L54 ANSWER 75 OF 132 MEDLINE on STN

2000113864. PubMed ID: 10649615. Rectal and vaginal immunization with a macromolecular multicomponent peptide **vaccine** candidate for **HIV**-1 infection induces **HIV**-specific protective immune responses. Kato H; Bukawa H; Hagiwara E; Xin K Q; Hamajima K; Kawamoto S; Sugiyama M; Sugiyama M; Noda E; Nishizaki M; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) Vaccine, (2000 Jan 18) 18 (13) 1151-60. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB An effective **vaccine** for **human immunodeficiency virus** (**HIV**) is

mucosal transmission of the virus. We have developed a macromolecular multicomponent peptide **vaccine** candidate, VC1. Both rectal and vaginal immunization of VC1 mixed with cholera toxin (CT) induced **HIV**-1-specific IgA antibody in mouse fecal extract solution and vaginal wash. These antibody productions were enhanced by the combination with IL-4 or GM-CSF expressing **plasmids**. Either fecal extract or vaginal wash solution from immunized mice inhibited production of **HIV**-1IIIB p24 protein. The mononuclear cells from spleen, intestinal lymph nodes, or Peyer's patches from VC1- and CT-immunized mice released IFN-gamma or IL-4, when these cells were co-cultured with VC1 antigen. In addition, the regional lymphoid cells from rectal and vaginal region of mice immunized with VC1 and CT also elicited a substantial level of **HIV**-1-specific **cytotoxic** T cell (**CTL**) response. This **CTL** response was enhanced by the addition of IL-12 expressing **plasmid**. Our results clearly demonstrated that both rectal and vaginal immunization could induce systemic and mucosal immunities specific for **HIV**-1.

L54 ANSWER 76 OF 132 MEDLINE on STN
2000051327. PubMed ID: 10583605. Immunomodulatory effect of a **plasmid** expressing CD40 ligand on **DNA vaccination** against **human immunodeficiency virus** type-1. Ihata A; Watabe S; Sasaki S; Shirai A; Fukushima J; Hamajima K; Inoue J; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) Immunology, (1999 Nov) 98 (3) 436-42. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB CD40 ligand is a costimulatory molecule which acts a potent immunomodulator. We found the mice inoculated with human CD40 ligand expression **plasmid** (pMEhCD40L) combined with **human immunodeficiency virus** type-1 (**HIV**-1) **DNA vaccine** exhibited both humoral and cellular antigen-specific immunological enhancement. The expression of hCD40L induced predominantly antigen-specific immunoglobulin G (IgG) antibody response while it failed to induce mucosal IgA response. Delayed-type hypersensitivity (DTH) and **cytotoxic** T lymphocyte (**CTL**) activity were induced in a dose-dependent manner. Examination of the relative levels of the two IgG subclasses showed that co-injection of pMEhCD40L enhanced IgG2a response without suppressing IgG1 response. Similarly, the expression of pMEhCD40L enhanced not only T helper 1 (Th1)-but also Th2-type cytokine production. In conclusion, co-inoculation of pMEhCD40L with **DNA vaccine** was shown to be a useful way to enhance **CTL** responses without suppressing the humoral immune response in acquired immune deficiency syndrome (AIDS) patients.

L54 ANSWER 77 OF 132 MEDLINE on STN
2000027246. PubMed ID: 10559335. Efficient processing of the immunodominant, HLA-A*0201-restricted **human immunodeficiency virus** type 1 **cytotoxic** T-lymphocyte epitope despite multiple variations in the epitope flanking sequences. Brander C; Yang O O; Jones N G; Lee Y; Goulder P; Johnson R P; Trocha A; Colbert D; Hay C; Buchbinder S; Bergmann C C; Zweerink H J; Wolinsky S; Blattner W A; Kalams S A; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.. brander@helix.mgh.harvard.edu) . Journal of virology, (1999 Dec) 73 (12) 10191-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Immune escape from **cytotoxic** T-lymphocyte (**CTL**) responses has been shown to occur not only by changes within the targeted epitope but also by changes in the flanking sequences which interfere with the processing of the immunogenic peptide. However, the frequency of such an escape mechanism has not been determined. To investigate whether naturally occurring variations in the flanking sequences of an immunodominant **human immunodeficiency virus** type 1 (**HIV**-1) Gag **CTL** epitope prevent antigen processing, cells infected with **HIV**-1 or **vaccinia** virus constructs encoding different patient-derived Gag sequences were tested for recognition by HLA-A*0201-restricted, p17-specific **CTL**. We found that the immunodominant p17 epitope (SL9) and its variants were

efficiently processed from minigene-expressing vectors and from SIV HIV-1 Gag variants expressed by recombinant **vaccinia** virus constructs. Furthermore, SL9-specific **CTL** clones derived from multiple donors efficiently inhibited virus replication when added to HLA-A*0201-bearing cells infected with primary or laboratory-adapted strains of virus, despite the variability in the SL9 flanking sequences. These data suggest that escape from this immunodominant **CTL** response is not frequently accomplished by changes in the epitope flanking sequences.

L54 ANSWER 78 OF 132 MEDLINE on STN

1999451180. PubMed ID: 10519935. Humoral and cellular immune responses to **HIV**-1 nef in mice **DNA**-immunised with non-replicating or self-replicating expression vectors. Collings A; Pitkanen J; Strengell M; Tahtinen M; Lagerstedt A; Hakkarainen K; Ovod V; Sutter G; Ustav M; Ustav E; Mannik A; Ranki A; Peterson P; Krohn K. (Institute of Medical Technology, University of Tampere, Tampere, Finland.) Vaccine, (1999 Oct 14) 18 (5-6) 460-7. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: **HIV** accessory protein Nef is expressed early in the infectious cycle of the virus and has been shown to be an effective immunogen in humoral and cellular immune responses. We have used two different self-replicating pBN vectors and one non-replicating pCGal2 derived (pCG) vector expressing **HIV**-1 Nef in **DNA** immunisation of mice in order to determine their efficiency in raising humoral and cellular immune responses. DESIGN AND METHODS: The expression of Nef by the three **plasmids** was tested by transfections into COS-1 cells. Balb/c mice were immunised with the pBN-NEF and pCGE2-NEF constructs using gold particle bombardment. Immunoblotting and immunocytochemistry were used to detect in vitro expression of Nef. 51Cr release assay, ELISA and immunoblotting were used to detect cellular and humoral immune responses in immunised mice. RESULTS: Efficient in vitro expression of Nef was detected in pBN and pCGE2-NEF transfected cells, in pBN-NEF transfected cells the expression lasting up to three weeks. Anti-Nef antibodies in sera of 13 of 16 pBN-NEF immunised mice were detected within four weeks after the last immunisation, whereas only 2 of 12 pCGE2-NEF immunised mice had very weak anti-Nef antibodies. Twelve of the pBN-NEF immunised mice (75%) and 6 the pCGE2-NEF immunised mice (50%) showed Nef-specific **cytotoxic** T lymphocyte (**CTL**) responses within four weeks. CONCLUSIONS: We conclude that the three eukaryotic expression vectors tested are capable of inducing a cell mediated immune response towards **HIV**-1 Nef and should be considered as part of a **genetic HIV vaccine**.

L54 ANSWER 79 OF 132 MEDLINE on STN

1999408865. PubMed ID: 10479171. Systemic and mucosal immunity is elicited after both intramuscular and intravaginal delivery of **human immunodeficiency virus** type 1 **DNA plasmid vaccines** to pregnant chimpanzees. Bagarazzi M L; Boyer J D; Javadian M A; Chattergoon M A; Shah A R; Cohen A D; Bennett M K; Ciccarelli R B; Ugen K E; Weiner D B. (MCP Hahnemann University, Department of Pediatrics, St. Christopher's Hospital for Children, Philadelphia, PA 19134, USA.. mark.bagarazzi@drexel.edu) . Journal of infectious diseases, (1999 Oct) 180 (4) 1351-5. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB **DNA vaccines** encoding **human immunodeficiency virus** type 1 (**HIV**-1) env/rev and gag/pol were delivered intravaginally (IVAG) and intramuscularly (IM) to 2 pregnant chimpanzees. **Vaccination** was well tolerated and each chimpanzee developed antibodies (up to 1 year later) to both **vaccines**. Placental transfer of anti-Env and anti-Gag IgG was demonstrated in both maternal/infant pairs. Specific IgG was also demonstrated in saliva, vaginal, and rectal washes after IVAG immunization. Predominantly anti-**HIV**-1 IgA was detected in the milk of both mothers after both IM and IVAG immunization. Cellular responses included Gag-specific proliferation of lymphocytes and **cytotoxic** T lymphocytes against both antigens. These data suggest a strategy for induction of mucosal and systemic responses after both IM and IVAG delivery of **DNA vaccines** in a primate model and could ultimately be useful in lowering maternal-to-fetal transmission of **HIV**-1, perinatally

and through breastfeeding.

L54 ANSWER 80 OF 132 MEDLINE on STN
1999370046. PubMed ID: 10438897. Immune responses in asymptomatic **HIV**-1-infected patients after **HIV-DNA** immunization followed by highly active antiretroviral treatment. Calarota S A; Leandersson A C; Bratt G; Hinkula J; Klinman D M; Weinhold K J; Sandstrom E; Wahren B. (Swedish Institute for Infectious Disease Control, Microbiology, Tumorbiology Center, Karolinska Institute, Stockholm.) Journal of immunology (Baltimore, Md. : 1950), (1999 Aug 15) 163 (4) 2330-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Intensive chemotherapy is capable of reducing the viral load in **HIV**-1-infected individuals while infected cells are still present. A special property of **DNA** immunization is to induce both new **CTL** and Ab responses. We evaluated the possibility of inducing new immune responses in already infected individuals by means of **DNA** constructs encoding the nef, rev, or tat regulatory **HIV**-1 genes. Significant changes in viral loads and CD4+ counts were observed in four patients who started highly active antiretroviral treatment (HAART) during the immunization study. The **DNA** immunization induced Ag-specific T cell proliferation, which persisted up to 9 mo after the last **DNA injection**, and cytolytic activities but did not, by itself, reduce viral load. Increased levels of **CTL** precursor cells were induced in all nine **DNA**-immunized patients. The profile of IFN-gamma secretion observed when human PBMC were transfected with the nef, rev, and tat **DNA** resembled that found in the **CTL** activity (nef > tat > rev). Ab responses that occurred after immunizations were of a low magnitude. In accordance with the high IL-6 production induced by the nef **DNA plasmid**, IgG titers were highest in patients immunized with nef **DNA**. The initiation of HAART appears to contribute to the induction of new **HIV**-specific **CTL** responses, but by itself did not cause obvious re-induction of these activities.

L54 ANSWER 81 OF 132 MEDLINE on STN
1999360933. PubMed ID: 10433551. **Genetic** live **vaccines** mimic the antigenicity but not pathogenicity of live viruses. Sykes K F; Johnston S A. (Center for Biomedical Inventions, Department of Internal Medicine, The University Texas-Southwestern Medical Center, Dallas 75235-8573, USA.. sykes@ryburn.swmed.edu) . DNA and cell biology, (1999 Jul) 18 (7) 521-31. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB The development of an effective **HIV vaccine** is both a pressing and a formidable problem. The most encouraging results to date have been achieved using live-attenuated immunodeficiency viruses. However, the frequency of pathogenic breakthroughs has been a deterrent to their development. We suggest that expression libraries generated from viral **DNA** can produce the immunologic advantages of live **vaccines** without risk of reversion to pathogenic viruses. The **plasmid** libraries could be deconvoluted into useful components or administered as complex mixtures. To explore this approach, we designed and tested several of these **genetic** live **vaccines** (GLVs) for **HIV**. We constructed libraries by cloning overlapping fragments of the proviral genome into mammalian expression **plasmids**, then used them to immunize mice. We found that inserting library fragments into a vector downstream of a secretory gene sequence led to augmented antibody responses, and insertion downstream of a ubiquitin sequence enhanced **cytotoxic** lymphocyte responses. Also, fragmentation of gag into subgenes broadened T-cell epitope recognition. We have fragmented the genome by sequence-directed and random methods to create libraries with different features. We propose that the characteristics of GLVs support their further investigation as an approach to protection against **HIV** and other viral pathogens.

L54 ANSWER 82 OF 132 MEDLINE on STN
1999345234. PubMed ID: 10418893. Xenogeneic and allogeneic anti-MHC immune responses induced by **plasmid DNA** immunization. Dela Cruz C S; Chamberlain J W; MacDonald K S; Barber B H. (Institute of Medical

17 (20-21) 2479-92. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Major histocompatibility complex (MHC) proteins are known to be incorporated into the **human immunodeficiency virus** (**HIV**-1) envelope as the virion buds from the host cell surface. Studies using simian immunodeficiency virus (SIV) infection of macaques have demonstrated that immunization with uninfected human cells or purified HLA proteins can provide protection from challenge with live SIV when it is grown in human cells expressing the same MHC alleles. Thus the induction of anti-MHC immune responses represents an important option to consider with respect to **vaccine** design for SIV and **HIV**. Here we examine **plasmid DNA** immunization strategies as an alternative to cellular or protein immunogens for the induction of xenogeneic and allogeneic immune responses in C57BL/6 mice and in an HLA transgenic mouse model system, respectively. We compared the immunogenicity of HLA-A2- and HLA-B27-expressing splenocytes with the corresponding **plasmid DNA** immunogens. Results from the transgenic mouse experiments indicate that **plasmid DNA** immunization with both **class I** and class II MHC-encoding vectors can elicit antibody responses recognizing conformationally intact MHC molecules. Our data also show that immunization with **class I** MHC-encoding **DNA** immunogens can elicit **cytotoxic** T-lymphocyte responses, demonstrating the potential to mobilize both antibody and cell-mediated anti-MHC immune responses in the context of this approach to **HIV**-1 **vaccine** design.

L54 ANSWER 83 OF 132 MEDLINE on STN

1999343954. PubMed ID: 10413656. Immunization of RANTES expression **plasmid** with a **DNA vaccine** enhances **HIV**-1-specific immunity. Xin K Q; Lu Y; Hamajima K; Fukushima J; Yang J; Inamura K; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Yokohama, 236, Japan.) Clinical immunology (Orlando, Fla.), (1999 Jul) 92 (1) 90-6. Journal code: 100883537. ISSN: 1521-6616. Pub. country: United States. Language: English.

AB Cytokines play important roles in regulating immune response. This study evaluated the adjuvant effect of an expression **plasmid** encoding RANTES (regulated on activation normal T-cell expressed and secreted) chemokine on the immunity induced by a **DNA vaccine**. This **vaccine** consists of expression **plasmids** encoding the env and rev genes of **human immunodeficiency virus** type 1 (**HIV**-1). **DNA vaccination** with RANTES **plasmid** induced significantly higher titers of serum **HIV**-1-specific IgG and IgG2a antibodies than **DNA vaccination** alone on both intramuscular and intranasal immunization. This combination also increased **HIV**-1-specific **cytotoxic** T lymphocyte activity and delayed-type hypersensitivity. Intranasal immunization induced a higher titer of fecal secretory IgA antibody than intramuscular immunization. These results demonstrate that coadministration of RANTES **plasmid** dominantly induced **HIV**-1-specific cell-mediated immunity.

L54 ANSWER 84 OF 132 MEDLINE on STN

1999294416. PubMed ID: 10367950. Gene gun **DNA vaccination** with Rev-independent synthetic **HIV**-1 gp160 envelope gene using mammalian codons. Vinner L; Nielsen H V; Bryder K; Corbet S; Nielsen C; Fomsgaard A. (Department of Virology, Statens Serum Institut, Copenhagen, Denmark.) Vaccine, (1999 Apr 23) 17 (17) 2166-75. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **DNA** immunization with **HIV** envelope **plasmids** induce only moderate levels of specific antibodies which may in part be due to limitations in expression influenced by a species-specific and biased **HIV** codon usage. We compared antibody levels, Th1/Th2 type and **CTL** responses induced by synthetic genes encoding membrane bound gp160 versus secreted gp120 using optimized codons and the efficient gene gun immunization method. The in vitro expression of syn.gp160 as gp120 + gp41 was Rev independent and much higher than a classical wt.gp160 **plasmid**. Mice immunized with syn.gp160 and wt.gp160 generated low and inconsistent ELISA antibody titres whereas

antibody titres. Due to a higher C + G content the numbers of putative CpG immune (Th1) stimulatory motifs were highest in the synthetic gp160 gene. However, both synthetic genes induced an equally strong and more pronounced Th2 response with higher IgG1/IgG2a and IFNgamma/IL-4 ratios than the wt.gp160 gene. As for induction of **CTL**, synthetic genes induced a somewhat earlier response but did not offer any advantage over wild type genes at a later time point. Thus, optimizing codon usage has the advantage of rendering the structural **HIV** genes Rev independent. For induction of antibodies the level of expression, while important, seems less critical than optimal contact with antigen presenting cells at locations reached by the secreted gp120 protein. A proposed Th1 adjuvant effect of the higher numbers of CpG motifs in the synthetic genes was not seen using gene gun immunization which may be due to the low amount of **DNA** used.

L54 ANSWER 85 OF 132 MEDLINE on STN
1999250814. PubMed ID: 10234555. The coming of age of tumour immunotherapy. Ada G. (Divison of Immunology and Cell Biology, John Curtin School of Medical Research, Australian National University, Canberra, Australia.) Immunology and cell biology, (1999 Apr) 77 (2) 180-5. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB Compared with the earlier incidence of acute infectious diseases, the introduction of **vaccines** has been one of the major public health success achievements. In contrast, **vaccine** development to control some persisting infections such as **HIV** remains a major challenge. There are many similarities with this task and that of controlling tumours by immunotherapy. Generating **CTL** responses by using pulsed dendritic cells has become a popular approach and has led to success with the mouse model. With viral antigens, priming with **DNA plasmids** and boosting with a chimeric live vector results in high levels of **CTL** activity, and is worth trying with cancer. A recent review highlights three other difficulties posed by tumours: epitope stability, maiming or killing of **CTL** by the tumour, and accessibility of the tumour vasculature to immune components. The new ability to label **CTL** by staining with specific tetrameric peptide/MHC complexes offers the possibility of effectively studying this third aspect. Our increased knowledge of tumour-associated antigens, viral or otherwise, and our growing ability to manipulate the immune system, offers hope that control of at least some human tumours may be within reach.

L54 ANSWER 86 OF 132 MEDLINE on STN
1999237851. PubMed ID: 10223340. **DNA-plasmids** of **HIV**-1 induce systemic and mucosal immune responses. Asakura Y; Lundholm P; Kjerrstrom A; Benthin R; Lucht E; Fukushima J; Schwartz S; Okuda K; Wahren B; Hinkula J. (Swedish Institute for Infectious Disease Control, Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm.) Biological chemistry, (1999 Mar) 380 (3) 375-9. Journal code: 9700112. ISSN: 1431-6730. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB **DNA-based** immunization has been shown to induce protective immunity against several microbial pathogens including **HIV**-1. Several routes of **DNA vaccination** have been exploited. However, the properties of the immune responses seem to differ with the different routes used for **DNA** delivery, ultimately affecting the outcome of experimental challenge. We measured the primary immune response following one **vaccination**. This report presents differences associated with three different **DNA** delivery routes: intramuscular injection, intranasal application, and gene-gun based immunization. Induction of systemic humoral immune responses was achieved most efficiently by either intranasal or gene-gun mediated immunization, followed by intramuscular injection. Mucosal IgA was reproducibly induced by intranasal instillation of the **DNA**, and found in lung washings, faeces, and vaginal washings. **Cytotoxic** T cells were not induced by a single immunization, but were observed after three immunizations using intramuscular injections.

L54 ANSWER 87 OF 132 MEDLINE on STN

1999217703. PubMed ID: 10203053. Protection from pathogenic SIV challenge using multigenic **DNA vaccines**. Haigwood N L; Pierce C C; Robertson M N; Watson A J; Montefiori D C; Rabin M; Lynch J B; Kuller L; Thompson J; Morton W R; Benveniste R E; Hu S L; Greenberg P; Mossman S P. (Seattle Biomedical Research Institute, WA 98109, USA.. haigwood@u.washington.edu) . Immunology letters, (1999 Mar) 66 (1-3) 183-8. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB To assess **DNA** immunization as a strategy for protecting against **HIV** infection in humans, we utilized SIVmne infection of Macaca fascicularis as a **vaccine** challenge model with moderate pathogenic potential. We compared the efficacy of **DNA** immunization alone and in combination with subunit protein boosts. All of the structural and regulatory genes of SIVmne clone 8 were cloned into mammalian expression vectors under the control of the CMV IE-1 promoter. Eight M. fascicularis were immunized twice with 3 mg of **plasmid DNA** divided between two sites; intramuscular and intradermal. Four primed macaques received a further two **DNA** immunizations at weeks 16-36, while the second group of four were boosted with 250 microg recombinant gp160 plus 250 microg recombinant Gag-Pol particles formulated in MF-59 adjuvant. Half of the controls received four immunizations of vector **DNA**; half received two vector **DNA** and two adjuvant immunizations. As expected, humoral immune responses were stronger in the macaques receiving subunit boosts, but responses were sustained in both groups. Significant neutralizing antibody titers to SIVmne were detected in one of the subunit-boosted animals and in none of the **DNA**-only animals prior to challenge. T-cell proliferative responses to gp160 and to Gag were detected in all immunized animals after three immunizations, and these responses increased after four immunizations. Cytokine profiles in PHA-stimulated PBMC taken on the day of challenge showed trends toward Thl responses in 2/4 macaques in the **DNA vaccinated** group and in 1/4 of the **DNA** plus subunit **vaccinated** macaques; Th2 responses in 3/4 **DNA** plus subunit-immunized macaques; and Th0 responses in 4/4 controls. In bulk **CTL** culture, SIV specific lysis was low or undetectable, even after four immunizations. However, stable SIV Gag-Pol- and env-specific T-cell clones (CD3+ CD8+) were isolated after only two **DNA** immunizations, and Gag-Pol- and Nef-specific **CTL** lines were isolated on the day of challenge. All animals were challenged at week 38 with SIVmne uncloned stock by the intrarectal route. Based on antibody anamnestic responses (western, ELISA, and neutralizing antibodies) and virus detection methods (co-culture of PBMC and LNMC, nested set PCR- of **DNA** from PBMC and LNMC, and plasma QC-PCR), there were major differences between the groups in the challenge outcome. Surprisingly, sustained low virus loads were observed only in the **DNA** group, suggesting that four immunizations with **DNA** only elicited more effective immune responses than two **DNA** primes combined with two protein boosts. Multigenic **DNA vaccines** such as these, bearing all structural and regulatory genes, show significant promise and may be a safe alternative to live-attenuated **vaccines**.

L54 ANSWER 88 OF 132 MEDLINE on STN

1999217702. PubMed ID: 10203052. Pre-clinical development of a multi-**CTL** epitope-based **DNA** prime MVA boost **vaccine** for AIDS. Hanke T; McMichael A. (Institute of Molecular Medicine, University of Oxford, The John Radcliffe Hospital, UK.. hanke@molbiol.ox.ac.uk) . Immunology letters, (1999 Mar) 66 (1-3) 177-81. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Reliable and effective methods for induction of **cytotoxic** T-lymphocytes (**CTL**) are constantly persued. Central to this search is work in animal models, which allow to test novel **vaccine** strategies and ultimately lead to a more efficient planning of clinical trials. Here, **human immunodeficiency virus** (**HIV**) **vaccine** candidates were constructed as a string of partially overlapping **CTL** epitopes (20 human, 3 macaque and 1 mouse) delivered and expressed using **plasmid DNA** and modified virus Ankara (MVA; an attenuated **vaccinia** virus), which are both **vaccine** vehicles acceptable for use in humans. In mice, these

vaccines were shown to induce virus-specific interferon gamma-producing and cytolytic CD8+ T-cells after a single intramuscular needle injection. When immunization protocols were sought which would improve the level of induced **HIV**-specific T-cells, **DNA** priming-MVA boosting was found to be the most potent protocol. The multi-epitope **DNA** also elicited **CTL** when delivered intradermally using the Accell gene delivery device (gene gun). Finally, a combined intradermal gene gun **DNA**-MVA **vaccination** regimen induced in macaques high frequencies of circulating **CTL**, which were comparable to those observed in simian immunodeficiency virus (SIV)-infected monkeys. Further optimization of this method in non-human primates is under way. Thus, a **vaccination** regimen for an effective elicitation of **CTL** has been developed which might facilitate evaluation of the role(s) that these lymphocytes play in the control of SIV and **HIV** infections.

L54 ANSWER 89 OF 132 MEDLINE on STN

1999196239. PubMed ID: 10098603. Improved immunogenicity of **HIV**-1 epitopes in HBsAg chimeric **DNA vaccine plasmids** by structural mutations of HBsAg. Bryder K; Sbai H; Nielsen H V; Corbet S; Nielsen C; Whalen R G; Fomsgaard A. (Department of Virology, Statens Serum Institut, Copenhagen, Denmark.) DNA and cell biology, (1999 Mar) 18 (3) 219-25. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB To improve the immunogenicity of epitopes from the envelope protein of **HIV**-1, we have developed gene gun-delivered subunit **DNA vaccines** by inserting the sequences encoding the V3 region into the hepatitis B virus (HBV) envelope gene, often called the surface antigen (HBsAg). We have examined the possibility of modifying the immune response to V3 by introducing modifications into the carrier HBsAg in gene gun **DNA** immunization of mice. In some **plasmid** constructions, the V3 sequence was introduced into the preS2 region of the HBsAg. Although this region is not present in all protein subunits of the HBsAg particles produced, abolishing the internal translational initiation site for the S protein had no effect on the immune response to V3. Expression of V3 at the N-terminal or C-terminal part of the HBsAg protein resulted in equal anti-V3 antibody and **cytotoxic** T-lymphocyte (**CTL**) responses. However, elimination of secretion by single amino-acid mutations in the HBsAg decreased the anti-HBsAg antibody response but enhanced the anti-V3 antibody response. In contrast, the **CTL** response to V3 was independent of the structural mutations but could be improved by a total deletion of the HBsAg sequence part. Thus, the immune response to heterologous epitopes can be altered by modifications in the carrier HBsAg protein. Modifications of the HBsAg carrier might interfere with the dominant immune response to the HBsAg epitopes, allowing better antibody induction to less immunogenic foreign epitopes. However, for induction of **CTL** responses, the expression of minimal epitopes may be advantageous.

L54 ANSWER 90 OF 132 MEDLINE on STN

1999165015. PubMed ID: 10067692. IL-15 expression **plasmid** enhances cell-mediated immunity induced by an **HIV**-1 **DNA vaccine**. Xin K Q; Hamajima K; Sasaki S; Tsuji T; Watabe S; Okada E; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Yokohama, Japan.) Vaccine, (1999 Feb 26) 17 (7-8) 858-66. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cytokines are powerful regulators of the immune response. In this study, an **HIV**-1 envelope **DNA vaccine** and interleukin 15 (IL-15) expression **plasmid** were intranasally administered to mice. A significant increase in the **HIV**-1-specific DTH response and **CTL** activity, and decrease in the serum IgG/IgG2a ratio was observed in the group which received **DNA vaccine** and IL-15 expression **plasmid** compared to **DNA vaccination** alone. Restimulated immune lymphoid cells from mice which received both agents showed enhanced production of interferon-gamma (IFN-gamma) and reduced secretion of IL-4. However, administration of **DNA vaccine** with IL-15 and IL-2 or IL-12 expression **plasmids** did not alter the effect of IL-15 expression **plasmid** on the **DNA vaccine**. These results indicate that intranasal administration of **DNA vaccine** and

IL-15 expression **plasmid** is capable of enhancing the T helper type 1 (Th1) dependent **HIV**-1-specific cell-mediated immunity, and that the IL-15 and IL-2 or IL-12 expression **plasmids** may not have a synergistic effect on the immune response induced by **DNA vaccine** in vivo.

L54 ANSWER 91 OF 132 MEDLINE on STN

1999132267. PubMed ID: 9933462. Macrophage inflammatory protein-1alpha (MIP-1alpha) expression **plasmid** enhances **DNA vaccine**-induced immune response against **HIV**-1. Lu Y; Xin K Q; Hamajima K; Tsuji T; Aoki I; Yang J; Sasaki S; Fukushima J; Yoshimura T; Toda S; Okada E; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Yokohama, Japan.) Clinical and experimental immunology, (1999 Feb) 115 (2) 335-41. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.

AB CD8+ cell-secreted CC-chemokines, MIP-1alpha, and MIP-beta have recently been identified as factors which suppress **HIV**. In this study we co-inoculated MIP-1alpha expression **plasmid** with a **DNA vaccine** constructed from **HIV**-1 pCMV160IIIB and pcREV, and evaluated the effect of the adjuvant on **HIV**-specific immune responses following intramuscular and intranasal immunization. The levels of both **cytotoxic** T lymphocyte (**CTL**) activity and DTH showed that **HIV**-specific cell-mediated immunity (CMI) was significantly enhanced by co-inoculation of the MIP-1alpha expression **plasmid** with the **DNA vaccine** compared with inoculation of the **DNA vaccine** alone. The **HIV**-specific serum IgG1/IgG2a ratio was significantly lowered when the **plasmid** was co-inoculated in both intramuscular and intranasal routes, suggesting a strong elicitation of the T helper (Th) 1-type response. When the MIP-1alpha expression **plasmid** was inoculated intramuscularly with the **DNA vaccine**, an infiltration of mononuclear cells was observed at the injection site. After intranasal administration, the level of mucosal secretory IgA antibody was markedly enhanced. These findings demonstrate that MIP-1alpha expression **plasmid** inoculated together with **DNA vaccine** acts as a strong adjuvant for eliciting Th1-derived immunity.

L54 ANSWER 92 OF 132 MEDLINE on STN

1999030931. PubMed ID: 9811759. Enhanced T-cell immunogenicity and protective efficacy of a **human immunodeficiency virus** type 1 **vaccine** regimen consisting of consecutive priming with **DNA** and boosting with recombinant fowlpox virus. Kent S J; Zhao A; Best S J; Chandler J D; Boyle D B; Ramshaw I A. (AIDS Pathogenesis Research Unit, Macfarlane Burnet Centre for Medical Research, Fairfield 3078, Victoria, Australia.. kent@burnet.edu.au) . Journal of virology, (1998 Dec) 72 (12) 10180-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The induction of **human immunodeficiency virus** (**HIV**)-specific T-cell responses is widely seen as critical to the development of effective immunity to **HIV** type 1 (**HIV**-1). **Plasmid DNA** and recombinant fowlpox virus (rFPV) **vaccines** are among the most promising safe **HIV**-1 **vaccine** candidates. However, the immunity induced by either **vaccine** alone may be insufficient to provide durable protection against **HIV**-1 infection. We evaluated a consecutive immunization strategy involving priming with **DNA** and boosting with rFPV **vaccines** encoding common **HIV**-1 antigens. In mice, this approach induced greater **HIV**-1-specific immunity than either vector alone and protected mice from challenge with a recombinant **vaccinia** virus expressing **HIV**-1 antigens. In macaques, a dramatic boosting effect on **DNA vaccine**-primed **HIV**-1-specific helper and **cytotoxic** T-lymphocyte responses, but a decline in **HIV**-1 antibody titers, was observed following rFPV immunization. The **vaccine** regimen protected macaques from an intravenous **HIV**-1 challenge, with the resistance most likely mediated by T-cell responses. These studies suggest a safe strategy for the enhanced generation of T-cell-mediated protective immunity to **HIV**-1.

L54 ANSWER 93 OF 132 MEDLINE on STN

1998444396. PubMed ID: 9767429. Intranasal administration of **human immunodeficiency virus** type-1 (**HIV**-1) **DNA vaccine** with

Interleukin-2 expression **plasmid** enhances cell-mediated immunity against **HIV**-1. Xin K Q; Hamajima K; Sasaki S; Honsho A; Tsuji T; Ishii N; Cao X R; Lu Y; Fukushima J; Shapshak P; Kawamoto S; Okuda K. (Department of Bacteriology, Yokohama City University School of Medicine, Japan.) Immunology, (1998 Jul) 94 (3) 438-44. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **DNA vaccine** against **human immunodeficiency virus** type-1 (**HIV**-1) can induce substantial levels of **HIV**-1-specific humoral and cell-mediated immunity. To develop more potent **HIV**-1 **DNA vaccine** formulations, we used a murine model to explore the immunomodulatory effects of an interleukin-2 (IL-2) expression **plasmid** on an **HIV**-1 **DNA vaccine** following intranasal administration of the combination. When the **vaccine** and expression **plasmid** were incorporated into cationic liposomes and administered to mice, the **HIV**-1-specific delayed-type hypersensitivity response and **cytotoxic** T lymphocyte activity were significantly increased. Restimulated immune lymphoid cells showed enhanced production of both IL-2 and interferon-gamma and reduced secretion of IL-4. The level of total antibody to **HIV**-1 antigen was not greatly changed by coadministration of the **DNA vaccine** and IL-2 expression **plasmid**. An analysis of serum **HIV**-1-specific IgG subclasses showed a significant drop in the IgG1/IgG2a ratio in the group that received the **plasmid-vaccine** combination. These results demonstrate that the IL-2 expression **plasmid** strongly enhances the **HIV**-1-specific immune response via activation of T helper type-1 cells.

L54 ANSWER 94 OF 132 MEDLINE on STN

1998435937. PubMed ID: 9764908. Replication-defective **HIV** as a **vaccine** candidate. Tung F Y; Rinaldo C R Jr; Montelaro R C. (Department of Infectious Disease and Microbiology, University of Pittsburgh, Pennsylvania 15261, USA.) AIDS research and human retroviruses, (1998 Sep 20) 14 (14) 1247-52. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Live attenuated **vaccines** prepared from simian immunodeficiency virus (SIV) have provided the best protective immunity in challenge experiments. In animals **vaccinated** with attenuated SIV, immune responses may be elicited owing to endogenous expression of native SIV proteins and/or antigen presentation in the native replication site of virus. However, replication-competent viral **vaccines** raise safety concerns for clinical trials in humans. To ensure the safety and maintain the immunogenicity of a live, attenuated **vaccine**, we have developed a replication-defective **HIV** pseudotyped with vesicular stomatitis virus G protein (VSV-G). The polymerase gene of **HIV** was truncated to construct the replication-defective **HIV**. This pseudotyped **HIV** can infect many cell types, including human and simian cells, and undergoes only one round of replication. Furthermore, antibody immune response can be detected in mice immunized with VSV-G-pseudotyped replication-defective **HIV**.

L54 ANSWER 95 OF 132 MEDLINE on STN

1998417547. PubMed ID: 9743560. The T cell repertoire primed by antiviral **vaccination** is influenced by self-tolerance. Paliard X; Doe B; Walker C M. (Chiron Corporation, 4560 Horton Street, Emeryville, California, 94608, USA.) Cellular immunology, (1998 Aug 25) 188 (1) 73-9. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB **Vaccination** can elicit CD8(+) **cytotoxic** T lymphocytes (**CTL**) that recognize peptides presented by **class I** MHC molecules. Relatively little is known, however, about the **genetic** factors that shape the repertoire of T cell clonotypes responding to any given epitope. We report here that H-2(b) mice immunized with a **plasmid DNA vaccine** or **vaccinia** virus encoding for **HIV**-1SF2p55gag elicit CD8(+) **CTL** against the H-2Db-restricted immunodominant epitope (pgagb). This response involved three different T cell populations based on their recognition of alloantigens: one that cross-reacted with the alloantigen H-2Ld, one that cross-reacted with H-2Kd, and one that did not cross-react with either H-2(d) or H-2(k) molecules. Using the TAP-deficient cell line T2-Ld, we showed that pgagb-specific **CTL** cross-react with H-2Ld and a yet unidentified self-peptide. In mice expressing H-2(b) and H-2(d)

HIVp55gag-specific **CTL** repertoire as a consequence of thymic deletion of the cross-reactive **CTL** repertoire. In (H-2(dxb))F1 mice heterogygosity at the MHC-I level prevented maturation of some but not all TCR combinations specific for H-2Db+pgagb, illustrating the concept that self-tolerance can influence the repertoire of antiviral T cells. Copyright 1998 Academic Press.

L54 ANSWER 96 OF 132 MEDLINE on STN
1998391635. PubMed ID: 9725796. Comparisons of **DNA**-mediated immunization procedures directed against surface glycoproteins of **human immunodeficiency virus** type-1 and hepatitis B virus. Fomsgaard A; Nielsen H V; Nielsen C; Johansson K; Machuca R; Bruun L; Hansen J; Buus S. (Department of Virology, Statens Serum Institut, Copenhagen, Denmark.) APMIS : acta pathologica, microbiologica, et immunologica Scandinavica, (1998 Jun) 106 (6) 636-46. Journal code: 8803400. ISSN: 0903-4641. Pub. country: Denmark. Language: English.

AB **DNA vaccination** methods were compared to examine the in vivo expression of **HIV**-1 gp160 and beta-galactosidase, and the resulting immune response. Beta-galactosidase **plasmid** showed expression rates of 2-5% of muscle fibers with or without pretreatments using bupivacaine or cardiotoxin facilitators 1 or 5 days earlier, respectively. In contrast, **HIV** gp160 expression was lower in untreated or bupivacaine-treated muscles, but was improved by pretreatment with cardiotoxin. Equal expression of beta-galactosidase and **HIV** gp160 was obtained using gene gun delivery to the epidermis. Unlike the i.m. in situ expression of gp160, the anti-**HIV** antibody response did not improve after muscle pretreatments but depended on the **vaccination** intervals. Gene gun delivery of pMN160 also resulted in a slow and low titered antibody response. In contrast, a single i.m. injection of **plasmid** encoding another viral envelope, HBsAg, resulted in earlier seroconversion to high titers without the need for pretreatments or boostings. Intradermal inoculation by gene gun using 100-fold less **DNA** resulted in the same anti-HBsAg antibody profile only after boostings. In contrast to the differences in antibody responses, a specific **CTL** response was obtained in all cases. Bupivacaine-treated muscles showed an extreme degree of edema with disruption of connective tissue (endo- and mesomysium) and was not well tolerated (4 of 19 mice died). Cardiotoxin created muscle necrosis and occasional (2 of 20 mice) development of fibrotic muscles. It is concluded that in vivo expression cannot be properly predicted using reporter gene experiments and that the resulting immune response does not follow directly with the expression rate. It is suggested that the antibody response may depend primarily on the nature of the antigen expressed rather than the **DNA vaccination** method. It is proposed that gene gun or i.m. injection be used without pretreatment in the case of **DNA vaccination** with **plasmid** encoding **HIV** MN gp160.

L54 ANSWER 97 OF 132 MEDLINE on STN
1998375874. PubMed ID: 9712056. Augmentation and suppression of immune responses to an **HIV**-1 **DNA vaccine** by **plasmid** cytokine/Ig administration. Barouch D H; Santra S; Steenbeke T D; Zheng X X; Perry H C; Davies M E; Freed D C; Craiu A; Strom T B; Shiver J W; Letvin N L. (Division of Viral Pathogenesis, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.) Journal of immunology (Baltimore, Md. : 1950), (1998 Aug 15) 161 (4) 1875-82. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The use of cytokines has shown promise as an approach for amplifying **vaccine**-elicited immune responses, but the application of these immunomodulatory molecules in this setting has not been systematically explored. In this report we investigate the use of protein- and **plasmid**-based cytokines to augment immune responses elicited by an **HIV**-1 gp120 **plasmid DNA vaccine** (pV1J-gp120) in mice. We demonstrate that immune responses elicited by pV1J-gp120 can be either augmented or suppressed by administration of **plasmid** cytokines. A dicistronic **plasmid** expressing both gp120 and IL-2 induced a surprisingly weaker gp120-specific immune response than did the

soluble IL-2/Ig fusion protein following pV1J-gp120 **vaccination** significantly amplified the gp120-specific immune response as measured by Ab, proliferative, and **CTL** levels. Administration of **plasmid** IL-2/Ig had different effects on the **DNA vaccine**-elicited immune response that depended on the temporal relationship between Ag and cytokine delivery. Injection of **plasmid** IL-2/Ig either before or coincident with pV1J-gp120 suppressed the gp120-specific immune response, whereas injection of **plasmid** IL-2/Ig after pV1J-gp120 amplified this immune response. To maximize immune responses elicited by a **DNA vaccine**, therefore, it appears that the immune system should first be primed with a specific Ag and then amplified with cytokines. The data also show that IL-2/Ig is more effective than native IL-2 as a **DNA vaccine** adjuvant.

L54 ANSWER 98 OF 132 MEDLINE on STN
1998296349. PubMed ID: 9632379. Progress in the development of an **HIV**-1 **vaccine**. Letvin N L. (The author is at Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.. nletvin@bidmc.harvard.edu) . Science, (1998 Jun 19) 280 (5371) 1875-80. Ref: 55. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Containment of the acquired immunodeficiency syndrome (AIDS) epidemic will require an effective **human immunodeficiency virus** type 1 (**HIV**-1) **vaccine**. Accumulating evidence suggests that such a **vaccine** must efficiently elicit an **HIV**-1-specific **cytotoxic** T lymphocyte (**CTL**) response. Nonhuman primate models will continue to provide an important tool for assessing the extent of protective immunity induced by various immunization strategies. Although replication-competent AIDS viruses attenuated for pathogenicity by selective gene deletions have provided protective immunity in nonhuman primate models, the long-term safety of such **vaccines** in human populations is suspect. Inactivated virus and subunit **vaccines** have elicited neither CTLs nor antibodies capable of neutralizing a wide array of patient **HIV**-1 isolates. Considerable effort is now being focused on evaluating live vector-based **vaccine** and **plasmid DNA vaccine** approaches for preventing **HIV**-1 infection both in animal model and human studies. Our growing understanding of the biology of **HIV**-1 and immune responses to this virus will continue to suggest improved **vaccination** approaches for exploration.

L54 ANSWER 99 OF 132 MEDLINE on STN
1998260936. PubMed ID: 9600309. Improved humoral and cellular immune responses against the gp120 V3 loop of **HIV**-1 following **genetic** immunization with a chimeric **DNA vaccine** encoding the V3 inserted into the hepatitis B surface antigen. Fomsgaard A; Nielsen H V; Bryder K; Nielsen C; Machuca R; Bruun L; Hansen J; Buus S. (Department of Virology, Statens Serum Institut, Copenhagen, Denmark.) Scandinavian journal of immunology, (1998 Apr) 47 (4) 289-95. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The gp120-derived V3 loop of **HIV**-1 is involved in co-receptor interaction, it guides cell tropism, and contains an epitope for antibody neutralization. Thus, **HIV**-1 V3 is an attractive **vaccine** candidate. The V3 of the MN strain (MN V3) contains both B- and T-cell epitopes, including a known mouse H-2d-restricted **cytotoxic** T lymphocyte (**CTL**) epitope. In an attempt to improve the immunogenicity of V3 in **DNA vaccines**, a **plasmid** expressing MN V3 as a fusion protein with the highly immunogenic middle (pre-S2 + S) surface antigen of hepatitis B virus (HBsAg) was constructed. Epidermal inoculation by gene gun was used for **genetic** immunization in a mouse model. Antibody and **CTL** responses to MN V3 and HBsAg were measured and compared with the immune responses obtained after **vaccination** with **plasmids** encoding the complete **HIV**-1 MN gp160 and HBsAg (pre-S2 + S), respectively. **DNA vaccination** with the **HIV** MN gp160 envelope **plasmid** induced a slow and low titred anti-MN V3 antibody response at 12 weeks post-inoculation (p.i.) and a late appearing (7 weeks), weak and variable **CTL** response. In contrast, **DNA vaccination** with the HBsAg-encoding **plasmid** induced a rapid and high titred anti-HBsAg antibody response and a uniform strong anti-HBs

CTL response already 1 week p.i. in all mice. DNA vaccination with the chimeric MN V3/HBsAg **plasmid** elicited humoral responses against both viruses within 3-6 weeks which peaked at 6-12 weeks and remained stable for at least 25 weeks. In addition, specific **CTL** responses were induced in all mice against both MN V3 and HBsAg already within the first 3 weeks, lasting at least 11 weeks. Thus, HBsAg acts as a **'genetic vaccine** adjuvant' augmenting and accelerating the cellular and humoral immune response against the inserted MN V3 loop. Such chimeric **HIV**-HBsAg **plasmid** constructs may be useful in **DNA** immunizations as a 'carrier' of protein regions or minimal epitopes which are less exposed or poorly immunogenic.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
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                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
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L27          101 S L26 NOT L20
                 E HEARD J M/AU
L28            7 S E8
L29            7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                 E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30         2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31         1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32          795 S L31 AND EXOGENOUS
L33          790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34           77 S L33 AND PLASMID/CLM
L35           11 S L34 AND PY<2002
L36           49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37          138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38           10 S L37 AND DENDRITIC
L39            1 S L38 AND (GENE VACCINATION)
L40          181 S (NAKED PLASMID DNA)
L41           11 S L40 AND PY=1996
L42            5 S L40 AND DENDRITIC
L43            0 S L40 AND (MULTIVALENT)
L44           80 S MULTIVALENT VACCINE
L45            1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46          162 S MULTIVALEN? VACCIN?
L47            6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48            0 S L46 AND (TWO PLASMIDS)
L49            1 S (MULTI-PLASMID DNA VACCINATION)
L50       140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51         7795 S L50 AND VACCIN?
L52          324 S L51 AND (PLASMID?)
L53          324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54          132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)

=> s (SIV or simian immunodeficiency virus)
          3763 SIV
         18945 SIMIAN
        112830 IMMUNODEFICIENCY
        373673 VIRUS
          2321 SIMIAN IMMUNODEFICIENCY VIRUS
                 (SIMIAN(W)IMMUNODEFICIENCY(W)VIRUS)
L55       4028 (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)

=> s l55 and vaccin?
        146418 VACCIN?
L56       1102 L55 AND VACCIN?

=> s l56 and plasmid?
         97133 PLASMID?
L57         70 L56 AND PLASMID?

=> s l57 and (CTL or cytotoxic or class I)
         11129 CTL
         81743 CYTOTOXIC
        171456 CLASS
       1140219 I
         32227 CLASS I
                 (CLASS(W)I)
L58         25 L57 AND (CTL OR CYTOTOXIC OR CLASS I)

=> s l58 not l54
L59          3 L58 NOT L54

=> d l59,cbib,ab,1-3
```

L59 ANSWER 1 OF 3 MEDLINE on STN

2002487220. PubMed ID: 12297408. Immune responses against **SIV** envelope glycoprotein, using recombinant SV40 as a **vaccine** delivery vector. McKee Hayley J; Strayer David S. (Department of Pathology and Cell Biology, Jefferson Medical College, 251 Jefferson Alumni Hall, 1020 Locust Street, Philadelphia, PA 19107, USA.) Vaccine, (2002 Oct 4) 20 (29-30) 3613-25. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB **Vaccination** protocols using viral gene delivery vectors have often generated relatively weak responses, largely owing to difficulties in boosting immune responses effectively following the primary injection. Because recombinant gene delivery vectors derived from SV40 permit multiple inoculations, to yield incremental immune responses, we tested the use of rSV40s to deliver lentiviral envelope antigens for immunization. An rSV40 carrying SIVmac239 envelope glycoprotein gp130 cDNA (SV(gp130)) was given multiple times to BALB/c mice, with or without a prior priming inoculation using **vaccinia** virus carrying the same **SIV** envelope cDNA (VVenvSIV). Sera from these mice were tested for antibodies binding gp130, applying a novel cell-based ELISA protocol that used as targets cloned P815 cells stably transfected with **plasmid**-derived gp130 cDNA. The same gp130-expressing clone of P815 cells, labeled with 51Cr was used as targets for direct lymphocyte-mediated cytolytic assays using spleen and popliteal lymph node cells as effectors. After six inoculations with SV(gp130), mice made detectable anti-gp130 antibody responses, but high levels of splenic and popliteal lymph node **cytotoxic** activity were apparent after as few as three injections of SV(gp130) (>40% specific lysis). A single primary inoculation with VVenvSIV preceding SV(gp130) boosts significantly enhanced antibody responses against **SIV** gp130, but had little effect on **cytotoxic** lymphocyte responses. Thus, rSV40 vectors may be useful vehicles for delivering lentiviral envelope antigens to elicit protective humoral and cell-mediated immune responses.

L59 ANSWER 2 OF 3 MEDLINE on STN

97053992. PubMed ID: 8898371. Induction of antigen-specific tumor immunity by genetic and cellular **vaccines** against MAGE: enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1. Bueler H; Mulligan R C. (Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts, USA.) Molecular medicine (Cambridge, Mass.), (1996 Sep) 2 (5) 545-55. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: A number of tumors express antigens that are recognized by specific **cytotoxic** T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and MAGE-3 are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular **vaccines** against MAGE-1 and MAGE-3 can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. MATERIALS AND METHODS: Mice were immunized against MAGE-1 and MAGE-3 by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein **SIV** tat, and tumor development and survival were monitored. RESULTS: Intramuscular expression of MAGE-1 and MAGE-3 by **plasmid** DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and MAGE-3. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (GM-CSF) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. CONCLUSIONS: Our results suggest that genetic and cellular **vaccines** against MAGE and other tumor antigens may be useful for the

therapy of tumors expressing specific markers, and that GM-CSF and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

L59 ANSWER 3 OF 3 MEDLINE on STN
96211533. PubMed ID: 8648735. **Simian immunodeficiency virus** DNA **vaccine** trial in macaques. Lu S; Arthos J; Montefiori D C; Yasutomi Y; Manson K; Mustafa F; Johnson E; Santoro J C; Wissink J; Mullins J I; Haynes J R; Letvin N L; Wyand M; Robinson H L. (Department of Pathology, University of Massachusetts Medical Center, Worcester 01655, USA.) Journal of virology, (1996 Jun) 70 (6) 3978-91. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB An experimental **vaccine** consisting of five DNA **plasmids** expressing different combinations and forms of **simian immunodeficiency virus**-macaque (SIVmac) proteins has been evaluated for the ability to protect against a highly pathogenic uncloned SIVmac251 challenge. One **vaccine plasmid** encoded nonreplicating SIVmac239 virus particles. The other four **plasmids** encoded secreted forms of the envelope glycoproteins of two T-cell-tropic relatives (SIVmac239 and SIVmac251) and one monocyte/macrophage-tropic relative (SIVmac316) of the uncloned challenge virus. Rhesus macaques were inoculated with DNA at 1 and 3, 11 and 13, and 21 and 23 weeks. Four macaques were inoculated intravenously, intramuscularly, and by gene gun inoculations. Three received only gene gun inoculations. Two control monkeys were inoculated with control **plasmids** by all three routes of inoculation. Neutralizing antibody titers of 1:216 to 1:768 were present in all of the **vaccinated** monkeys after the second cluster of inoculations. These titers were transient, were not boosted by the third cluster of inoculations, and had fallen to 1:24 to 1:72 by the time of challenge. **Cytotoxic** T-cell activity for Env was also raised in all of the **vaccinated** animals. The temporal appearance of **cytotoxic** T cells was similar to that of antibody. However, while antibody responses fell with time, **cytotoxic** T-cell responses persisted. The SIVmac251 challenge was administered intravenously at 2 weeks following the last immunization. The DNA immunizations did not prevent infection or protect against CD4+ cell loss. Long-term chronic levels of infection were similar in the **vaccinated** and control animals, with 1 in 10,000 to 1 in 100,000 peripheral blood cells carrying infectious virus. However, viral loads were reduced to the chronic level over a shorter period of time in the **vaccinated** groups (6 weeks) than in the control group (12 weeks). Thus, the DNA **vaccine** raised both neutralizing antibody and **cytotoxic** T-lymphocyte responses and provided some attenuation of the acute phase of infection, but it did not prevent the loss of CD4+ cells.

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=> s l58 not l59
L60          22 L58 NOT L59

=> d l60,cbib,ab,1-22
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L60 ANSWER 1 OF 22 MEDLINE on STN
2003446446. PubMed ID: 12951017. Mucosal immunization with PLGA-microencapsulated DNA primes a **SIV**-specific **CTL** response revealed by boosting with cognate recombinant modified **vaccinia** virus Ankara. Sharpe Sally; Hanke Tomas; Tinsley-Bown Anne; Dennis Mike; Dowall Stuart; McMichael Andrew; Cranage Martin. (Health Protection Agency, Porton Down, Salisbury, Wiltshire, SP4 0JG, UK.. sally.sharpe@hpa.org.uk) . Virology, (2003 Aug 15) 313 (1) 13-21. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Systemically administered DNA encoding a recombinant human immunodeficiency virus (HIV) derived immunogen effectively primes a **cytotoxic** T lymphocyte (**CTL**) response in macaques. In this further pilot study we have evaluated mucosal delivery of DNA as an alternative priming strategy. **Plasmid** DNA, pTH.HW, encoding a multi-**CTL** epitope gene, was incorporated into poly(D,L-lactic-co-glycolic acid) microparticles of less than 10 microm in diameter. Five intrarectal

immunizations failed to stimulate a circulating vaccine-specific CTL response in 2 Mamu-A*01(+) rhesus macaques. However, 1 week after intradermal immunization with a cognate modified **vaccinia** virus Ankara **vaccine** MVA.HW, **CTL** responses were detected in both animals that persisted until analysis postmortem, 12 weeks after the final boost. In contrast, a weaker and less durable response was seen in an animal **vaccinated** with the MVA construct alone. Analysis of lymphoid tissues revealed a disseminated **CTL** response in peripheral and regional lymph nodes but not the spleen of both mucosally primed animals.

L60 ANSWER 2 OF 22 MEDLINE on STN
2003403481. PubMed ID: 12941922. Magnitude and diversity of **cytotoxic**-T-lymphocyte responses elicited by multiepitope DNA **vaccination** in rhesus monkeys. Subbramanian Ramu A; Kuroda Marcelo J; Charini William A; Barouch Dan H; Costantino Cristina; Santra Sampa; Schmitz Jorn E; Martin Kristi L; Lifton Michelle A; Gorgone Darci A; Shiver John W; Letvin Norman L. (Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Research East-RE 113, 330 Brookline Avenue, Boston, MA 02215, USA.) Journal of virology, (2003 Sep) 77 (18) 10113-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In an effort to develop an AIDS **vaccine** that elicits high-frequency **cytotoxic**-T-lymphocyte (**CTL**) responses with specificity for a diversity of viral epitopes, we explored two prototype multiepitope **plasmid** DNA **vaccines** in the simian-human immunodeficiency virus/rhesus monkey model to determine their efficiency in priming for such immune responses. While a simple multiepitope **vaccine** construct demonstrated limited immunogenicity in monkeys, this same multiepitope genetic sequence inserted into an immunogenic **simian immunodeficiency virus** gag DNA **vaccine** elicited high-frequency **CTL** responses specific for all of the epitopes included in the **vaccine**. Both multiepitope **vaccine** prototypes primed for robust epitope-specific **CTL** responses that developed following boosting with recombinant modified **vaccinia** virus Ankara **vaccines** expressing complete viral proteins. The natural hierarchy of immunodominance for these epitopes was clearly evident in the boosted monkeys. These studies suggest that multiepitope **plasmid** DNA **vaccine**-based prime-boost regimens can efficiently prime for **CTL** responses of increased breadth and magnitude, although they do not overcome predicted hierarchies of immunodominance.

L60 ANSWER 3 OF 22 MEDLINE on STN
2003354136. PubMed ID: 12867656. DNA **vaccination** of macaques by a full-genome simian/human immunodeficiency virus type 1 **plasmid** chimera that produces non-infectious virus particles. Akahata Wataru; Ido Eiji; Akiyama Hisashi; Uesaka Hiromi; Enose Yoshimi; Horiuchi Reii; Kuwata Takeo; Goto Toshiyuki; Takahashi Hidemi; Hayami Masanori. (Laboratory of Viral Pathogenesis, Institute for Virus Research, Kyoto University, Kyoto 606-8507, Japan.) Journal of general virology, (2003 Aug) 84 (Pt 8) 2237-44. Journal code: 0077340. ISSN: 0022-1317. Pub. country: England: United Kingdom. Language: English.

AB A DNA **vaccination** regime was investigated previously in rhesus macaques using a full-genome human immunodeficiency virus type 1 (HIV-1) **plasmid**, which, due to mutations in the nucleocapsid (NC) proteins, produced only non-infectious HIV-1 particles (Akahata et al., Virology 275, 116-124, 2000). In that study, four monkeys were injected intramuscularly 14 times with the **plasmid**. All of them showed immunological responses against HIV-1 and partial protection from challenge with a **simian immunodeficiency virus**/HIV (SHIV) chimeric virus. To improve this DNA **vaccination** regime, the **plasmid** used for **vaccination** was changed. In the present study, four macaques were injected intramuscularly eight times with a full-genome SHIV **plasmid** that produces non-infectious SHIV particles. **CTL** activities were higher than those observed in monkeys **vaccinated** previously with the HIV-1 **plasmid**. In all macaques **vaccinated**, peak plasma virus loads after homologous challenge with SHIV were two to three orders of magnitude lower than those of the naive controls, and virus loads fell below the level of detection at 6 weeks

post challenge. This suggested that the **vaccination** regime in this study was partially effective and better than the previous regime.

L60 ANSWER 4 OF 22 MEDLINE on STN
2002651164. PubMed ID: 12388710. Elicitation of **simian immunodeficiency virus**-specific **cytotoxic** T lymphocytes in mucosal compartments of rhesus monkeys by systemic **vaccination**. Baig Jamal; Levy Daniel B; McKay Paul F; Schmitz Joern E; Santra Sampa; Subbramanian Ramu A; Kuroda Marcelo J; Lifton Michelle A; Gorgone Darci A; Wyatt Linda S; Moss Bernard; Huang Yue; Chakrabarti Bimal K; Xu Ling; Kong Wing-Pui; Yang Zhi-Yong; Mascola John R; Nabel Gary J; Carville Angela; Lackner Andrew A; Veazey Ronald S; Letvin Norman L. (Division of Viral Pathogenesis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.) Journal of virology, (2002 Nov) 76 (22) 11484-90. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Since most human immunodeficiency virus (HIV) infections are initiated following mucosal exposure to the virus, the anatomic containment or abortion of an HIV infection is likely to require **vaccine**-elicited cellular immune responses in those mucosal sites. Studying **vaccine**-elicited mucosal immune responses has been problematic because of the difficulties associated with sampling T lymphocytes from those anatomic compartments. In the present study, we demonstrate that mucosal **cytotoxic** T lymphocytes (**CTL**) specific for **simian immunodeficiency virus** (**SIV**) and simian HIV can be reproducibly sampled from intestinal mucosal tissue of rhesus monkeys obtained under endoscopic guidance. These lymphocytes recognize peptide-major histocompatibility complex **class I** complexes and express gamma interferon on exposure to peptide antigen. Interestingly, systemic immunization of monkeys with **plasmid** DNA immunogens followed by live recombinant attenuated poxviruses or adenoviruses with genes deleted elicits high-frequency **SIV**-specific **CTL** responses in these mucosal tissues. These studies therefore suggest that systemic delivery of potent HIV immunogens may suffice to elicit substantial mucosal **CTL** responses.

L60 ANSWER 5 OF 22 MEDLINE on STN
2002632768. PubMed ID: 12390540. Inclusion of Vpr accessory gene in a **plasmid vaccine** cocktail markedly reduces Nef **vaccine** effectiveness in vivo resulting in CD4 cell loss and increased viral loads in rhesus macaques. Muthumani K; Bagarazzi M; Conway D; Hwang D S; Ayyavoo V; Zhang D; Manson K; Kim J; Boyer J; Weiner D B. (Department of Pathology & Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.) Journal of medical primatology, (2002 Aug) 31 (4-5) 179-85. Journal code: 0320626. ISSN: 0047-2565. Pub. country: Denmark. Language: English.

AB We compared the immunogenicity of **plasmid vaccines** containing multiple human immunodeficiency virus (HIV) antigens and found that covaccination with **plasmids** expressing HIV-1 14 kDa vpr gene product profoundly reduces antigen-specific CD8-mediated **cytotoxic** T-cell activity (**CTL**). Interestingly, Th1 type responses against codelivered antigens (pGag-Pol, pNef, etc.) encoded by the **plasmid vaccines** were suppressed. This suggested that vpr might compromise CD8 T-cell immunity in vivo during infection. A pilot primate **vaccine** study was designed to test the hypothesis to compare the following groups: unvaccinated controls, animals **vaccinated** without simean immunodeficiency virus (**SIV**)-Nef antigen **plasmid**, and animals covaccinated with the identical **plasmid** antigen and a **plasmid** construct encoding **SIV** Vpr/Vpx. Animals were subsequently challenged intrarectally with pathogenic SIVmac251 after the final **vaccination** of a multiple immunization protocol. Control animals were all infected and exhibited high viral loads and rapid CD4+ T-cell loss. In contrast, the Nef **plasmid-vaccinated** animals were also infected but exhibited preservation of CD4+ T-cells and a multilog reduction in viral load compared with controls. Animals covaccinated multiple times with the Nef **vaccine** and pVpr/Vpx **plasmid** suffered rapid and profound loss of CD4+ T-cells. These results have important implications for the design of multicomponent and particle **vaccines** for

HIV-1 as well as for our understanding of HIV/SIV pathogenesis in vivo.

L60 ANSWER 6 OF 22 MEDLINE on STN
2002299944. PubMed ID: 12021371. Prior **vaccination** increases the epitopic breadth of the **cytotoxic** T-lymphocyte response that evolves in rhesus monkeys following a simian-human immunodeficiency virus infection. Santra Sampa; Barouch Dan H; Kuroda Marcelo J; Schmitz Jorn E; Krivulka Georgia R; Beaudry Kristin; Lord Carol I; Lifton Michelle A; Wyatt Linda S; Moss Bernard; Hirsch Vanessa M; Letvin Norman L. (Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.) Journal of virology, (2002 Jun) 76 (12) 6376-81. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Although recent evidence has confirmed the importance of **cytotoxic** T-lymphocyte (**CTL**) responses in controlling human immunodeficiency virus type 1 and **simian immunodeficiency virus** replication, the relevance of the epitopic breadth of those **CTL** responses remains unexplored. In the present study, we sought to determine whether **vaccination** can expand **CTL** populations which recognize a repertoire of viral epitopes that is greater than is typically generated in the course of a viral infection. We demonstrate that potent secondary **CTL** responses to subdominant epitopes are rapidly generated following a pathogenic simian-human immunodeficiency virus challenge of rhesus monkeys **vaccinated** with **plasmid** DNA or recombinant modified **vaccinia** virus Ankara **vaccines**. These data indicate that prior **vaccination** can increase the breadth of the **CTL** response that evolves after an AIDS virus infection.

L60 ANSWER 7 OF 22 MEDLINE on STN
2001668256. PubMed ID: 11713828. Cytokine-induced augmentation of DNA **vaccine**-elicited **SIV**-specific immunity in rhesus monkeys. Barouch D H; Letvin N L. (Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.) Developments in biologicals, (2000) 104 85-92. Journal code: 100940058. ISSN: 1424-6074. Pub. country: Switzerland. Language: English.

AB **Plasmid** DNA **vaccination** has recently emerged as a promising approach to elicit HIV- and **SIV**-specific humoral and cellular immune responses. However, the magnitude of immune responses induced by DNA **vaccines** alone has not been sufficient to protect primates against pathogenic lentivirus challenges. We investigated the ability of an IL-2/lg cytokine fusion protein and a **plasmid** expressing IL-2/lg to augment immune responses in rhesus monkeys induced by DNA **vaccines** encoding **SIV** gag and HIV-1 env 89.6P. We showed that both IL-2/lg protein and IL-2/lg **plasmid** augment DNA **vaccine**-elicited antibody and **CTL** responses. The most consistent and dramatic augmentation was observed using the IL-2/lg **plasmid**.

L60 ANSWER 8 OF 22 MEDLINE on STN
2001409102. PubMed ID: 11257383. Modulation of antigen-specific cellular immune responses to DNA **vaccination** in rhesus macaques through the use of IL-2, IFN-gamma, or IL-4 gene adjuvants. Kim J J; Yang J S; Manson K H; Weiner D B. (Viral Genomix, Inc., Philadelphia, PA 19104, USA.) Vaccine, (2001 Mar 21) 19 (17-19) 2496-505. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Extensive experiments have shown DNA **vaccines'** ability to elicit immune responses in vivo in a safe and well-tolerated manner in several model systems, including rodents and non-human primates. As the DNA-based **vaccine** and immunotherapy approaches are being explored in humans, significant efforts have also been focused on further improving the immune potency of this technology. One strategy to enhance immune responses for DNA **vaccines** is the use of molecular or genetic adjuvants. These molecular adjuvant constructs (which encodes for immunologically important molecules such as cytokines) can be co-administered along with DNA **vaccine** constructs. Once delivered, these adjuvants have shown to modulate the magnitude and direction (humoral or cellular) of the **vaccine**-induced immune responses in rodent models. To date, however, there has been very little data reported from studies in primates. In this study, we examined the effects of cytokine gene adjuvants to enhance

the level of cell-mediated immune responses in rhesus macaques. We co-immunized rhesus macaques with expression **plasmids** encoding for IL-2, IFN-gamma or IL-4 cytokines along with the DNA **vaccine** constructs encoding for HIV env/rev (pCEnv) and **SIV** gag/pol (pCSGag/pol) proteins. We observed that coadministration of IL-2 and IFN-gamma cDNA resulted in enhancement of antigen-specific T cell-mediated immune responses.

L60 ANSWER 9 OF 22 MEDLINE on STN
2001409101. PubMed ID: 11257382. Expansion of HBV-specific memory **CTL** primed by dual HIV/HBV genetic immunization during SHIV primary infection in rhesus macaques. Borgne S L; Michel M L; Camugli S; Corre B; Le Grand R; Riviere Y. (Departement des Retrovirus, Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, 28, rue du Docteur Roux, 75724 Cedex 15, Paris, France.) Vaccine, (2001 Mar 21) 19 (17-19) 2485-95. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB We have previously shown the induction of humoral and **cytotoxic** responses specific for human immunodeficiency virus (HIV) and hepatitis B virus (HBV) antigens, following genetic immunization of rhesus macaques with a **plasmid** encoding both the third variable domain of the HIV-1 external envelope glycoprotein and the pseudo-viral particle of hepatitis B surface antigen (HBsAg) as presenting molecules. The DNA-immunized primates and two control animals were then challenged with a chimeric simian/human immunodeficiency virus (SHIV). They were all infected. Significant frequencies of SHIV specific **cytotoxic** T lymphocyte precursors (CTLp) were detected early in peripheral blood. But, in all DNA-immunized macaques, HBV envelope specific CTLp were detected during the primary infection, and they were correlated with the peak of SHIV viremia. Furthermore, HBV or SHIV specific cytotoxicity corresponded in part to CD8(+) T cells presenting a memory phenotype. Several mechanisms could account for this cellular response. But our results suggest that an expansion of memory **cytotoxic** CD8(+) cells, not restricted to SHIV specific effectors, could occur in peripheral blood during SHIV primary infection.

L60 ANSWER 10 OF 22 MEDLINE on STN
2001180944. PubMed ID: 11160750. Elicitation of high-frequency **cytotoxic** T-lymphocyte responses against both dominant and subdominant simian-human immunodeficiency virus epitopes by DNA **vaccination** of rhesus monkeys. Barouch D H; Craiu A; Santra S; Egan M A; Schmitz J E; Kuroda M J; Fu T M; Nam J H; Wyatt L S; Lifton M A; Krivulka G R; Nickerson C E; Lord C I; Moss B; Lewis M G; Hirsch V M; Shiver J W; Letvin N L. (Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. dan_barouch@hotmail.com) . Journal of virology, (2001 Mar) 75 (5) 2462-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Increasing evidence suggests that the generation of **cytotoxic** T-lymphocyte (**CTL**) responses specific for a diversity of viral epitopes will be needed for an effective human immunodeficiency virus type 1 (HIV-1) **vaccine**. Here, we determine the frequencies of **CTL** responses specific for the **simian immunodeficiency virus** Gag p11C and HIV-1 Env p41A epitopes in simian-human immunodeficiency virus (SHIV)-infected and **vaccinated** rhesus monkeys. The p11C-specific **CTL** response was high frequency and dominant and the p41A-specific **CTL** response was low frequency and subdominant in both SHIV-infected monkeys and in monkeys **vaccinated** with recombinant modified **vaccinia** virus Ankara vectors expressing these viral antigens. Interestingly, we found that **plasmid** DNA **vaccination** led to high-frequency **CTL** responses specific for both of these epitopes. These data demonstrate that **plasmid** DNA may be useful in eliciting a broad **CTL** response against multiple epitopes.

L60 ANSWER 11 OF 22 MEDLINE on STN
2001133497. PubMed ID: 11145897. DNA **vaccination** of macaques with several different Nef sequences induces multispecific T cell responses. Couillin I; Letourneur F; Lefebvre P; Guillet J G; Martinon F. (Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales,

Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States.
Language: English.

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary human immunodeficiency virus-1 and in maintaining disease-free infection. It has recently been shown that DNA immunization of rhesus monkeys can elicit strong, long-lived antigen-specific **cytotoxic** T lymphocyte (**CTL**) responses. In previous work, it was shown that macaque **CTL** responses to lipopeptide **vaccination** were directed against a limited number of epitopes. In the present study, we used the DNA immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six **plasmids** reflecting the variability of Nef epitopic regions in the **simian immunodeficiency virus** (**SIV**) mac251 primary isolate. The Nef genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that DNA immunization with Nef sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of Nef. Reacting T cell lines were expanded in vitro and multispecific **CTL** responses mapping the 96-138 Nef region were analyzed. Several peptides recognized by **CTL** were identified and studies using peptides reflecting the variability of Nef indicated that all of the Nef variants were recognized in the 96-138 region. Moreover, **CTL** responses were directed against an immunodominant epitope located in a functional region within the Nef protein that is essential for viral replication. This work shows that our approach of DNA immunization with several sequences induced multispecific T cell responses recognizing variants included in the SIVmac251 primary isolate.
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L60 ANSWER 12 OF 22 MEDLINE on STN
2000490347. PubMed ID: 11039923. Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA **vaccination**. Barouch D H; Santra S; Schmitz J E; Kuroda M J; Fu T M; Wagner W; Bilska M; Craiu A; Zheng X X; Krivulka G R; Beaudry K; Lifton M A; Nickerson C E; Trigona W L; Punt K; Freed D C; Guan L; Dubey S; Casimiro D; Simon A; Davies M E; Chastain M; Strom T B; Gelman R S; Montefiori D C; Lewis M G; Emini E A; Shiver J W; Letvin N L. (Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA.. dan_barouch@hotmail.com) . Science, (2000 Oct 20) 290 (5491) 486-92. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB With accumulating evidence indicating the importance of **cytotoxic** T lymphocytes (CTLs) in containing human immunodeficiency virus-1 (HIV-1) replication in infected individuals, strategies are being pursued to elicit virus-specific CTLs with prototype HIV-1 **vaccines**. Here, we report the protective efficacy of **vaccine**-elicited immune responses against a pathogenic SHIV-89.6P challenge in rhesus monkeys. Immune responses were elicited by DNA **vaccines** expressing SIVmac239 Gag and HIV-1 89.6P Env, augmented by the administration of the purified fusion protein IL-2/Ig, consisting of interleukin-2 (IL-2) and the Fc portion of immunoglobulin G (IgG), or a **plasmid** encoding IL-2/Ig. After SHIV-89.6P infection, sham-**vaccinated** monkeys developed weak **CTL** responses, rapid loss of CD4+ T cells, no virus-specific CD4+ T cell responses, high setpoint viral loads, significant clinical disease progression, and death in half of the animals by day 140 after challenge. In contrast, all monkeys that received the DNA **vaccines** augmented with IL-2/Ig were infected, but demonstrated potent secondary **CTL** responses, stable CD4+ T cell counts, preserved virus-specific CD4+ T cell responses, low to undetectable setpoint viral loads, and no evidence of clinical disease or mortality by day 140 after challenge.

L60 ANSWER 13 OF 22 MEDLINE on STN
2000407911. PubMed ID: 10856795. Anti-major histocompatibility complex antibody responses in macaques via intradermal DNA immunizations. Dela

Medical Sciences Building, University of Toronto, 1 King's College Circle, Ontario, M5S 1A8, Toronto, Canada.) Vaccine, (2000 Jul 15) 18 (27) 3152-65. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In **simian immunodeficiency virus** (**SIV**) models, immunization of macaques with uninfected human cells or human major histocompatibility complex (MHC) proteins can induce xenogeneic immune responses which can protect the animals from subsequent **SIV** challenges. These studies suggest that the induction of anti-MHC immune responses can be a viable **vaccine** strategy against human immunodeficiency virus type 1 (HIV-1). We have previously shown in mouse studies that DNA immunization with **class I** and class II MHC-encoding **plasmids** can elicit both xenogeneic and allogeneic antibody responses against conformationally intact MHC molecules (**Vaccine** 17 (1999) 2479-92). Here we take these observations one step closer to human applications and report that intradermal needle immunizations of non-human primates with **plasmid** DNA encoding human MHC alleles can safely elicit xenogeneic anti-MHC antibody responses. Moreover, injecting macaques with DNA encoding a specific macaque allogeneic MHC induced anti-allogeneic MHC antibodies production. These studies show that DNA immunization with MHC-encoding vectors can indeed be used to induce specific anti-human xenogeneic, as well as anti-macaque allogeneic MHC immunity in non-human primates. This strategy could thus be used to mobilize anti-MHC antibody response which may be useful as part of an anti-HIV-1 **vaccination** approach.

L60 ANSWER 14 OF 22 MEDLINE on STN
2000405861. PubMed ID: 10906202. **Simian immunodeficiency virus** (**SIV**) gag DNA-**vaccinated** rhesus monkeys develop secondary **cytotoxic** T-lymphocyte responses and control viral replication after pathogenic **SIV** infection. Egan M A; Charini W A; Kuroda M J; Schmitz J E; Racz P; Tenner-Racz K; Manson K; Wyand M; Lifton M A; Nickerson C E; Fu T; Shiver J W; Letvin N L. (Division of Viral Pathogenesis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. eganm@WAR.Wyeth.com) . Journal of virology, (2000 Aug) 74 (16) 7485-95. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The potential contribution of a **plasmid** DNA construct to **vaccine**-elicited protective immunity was explored in the **simian immunodeficiency virus** (**SIV**)/macaque model of AIDS. Making use of soluble major histocompatibility **class I**/peptide tetramers and peptide-specific killing assays to monitor CD8(+) T-lymphocyte responses to a dominant **SIV** Gag epitope in genetically selected rhesus monkeys, a codon-optimized **SIV** gag DNA **vaccine** construct was shown to elicit a high-frequency **SIV**-specific **cytotoxic** T-lymphocyte (**CTL**) response. This **CTL** response was demonstrable in both peripheral blood and lymph node lymphocytes. Following an intravenous challenge with the highly pathogenic viral isolate SIVsm E660, these **vaccinated** monkeys developed a secondary **CTL** response that arose with more rapid kinetics and reached a higher frequency than did the postchallenge **CTL** response in control **plasmid-vaccinated** monkeys. While peak plasma **SIV** RNA levels were comparable in the experimentally and control-**vaccinated** monkeys during the period of primary infection, the gag **plasmid** DNA-**vaccinated** monkeys demonstrated better containment of viral replication by 50 days following **SIV** challenge. These findings indicate that a **plasmid** DNA **vaccine** can elicit **SIV**-specific **CTL** responses in rhesus monkeys, and this **vaccine**-elicited immunity can facilitate the generation of secondary **CTL** responses and control of viral replication following a pathogenic **SIV** challenge. These observations suggest that **plasmid** DNA may prove a useful component of a human immunodeficiency virus type 1 **vaccine**.

L60 ANSWER 15 OF 22 MEDLINE on STN
2000226080. PubMed ID: 10759543. Augmentation of immune responses to HIV-1 and **simian immunodeficiency virus** DNA **vaccines** by IL-2/Ig **plasmid** administration in rhesus monkeys. Barouch D H; Craiu A; Kuroda M

Crabbs C L; Heidecker G; Perry H C; Davies M E; Xie H; Nickerson C E; Steenbeke T D; Lord C I; Montefiori D C; Strom T B; Shiver J W; Lewis M G; Letvin N L. (Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2000 Apr 11) 97 (8) 4192-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The potential utility of **plasmid** DNA as an HIV-1 **vaccination** modality currently is an area of active investigation. However, recent studies have raised doubts as to whether **plasmid** DNA alone will elicit immune responses of sufficient magnitude to protect against pathogenic AIDS virus challenges. We therefore investigated whether DNA **vaccine**-elicited immune responses in rhesus monkeys could be augmented by using either an IL-2/Ig fusion protein or a **plasmid** expressing IL-2/Ig. Sixteen monkeys, divided into four experimental groups, were immunized with (i) sham **plasmid**, (ii) HIV-1 Env 89.6P and **simian immunodeficiency virus** mac239 Gag DNA **vaccines** alone, (iii) these DNA **vaccines** and IL-2/Ig protein, or (iv) these DNA **vaccines** and IL-2/Ig **plasmid**. The administration of both IL-2/Ig protein and IL-2/Ig **plasmid** induced a significant and sustained in vivo activation of peripheral T cells in the **vaccinated** monkeys. The monkeys that received IL-2/Ig **plasmid** generated 30-fold higher Env-specific antibody titers and 5-fold higher Gag-specific, tetramer-positive CD8+ T cell levels than the monkeys receiving the DNA **vaccines** alone. IL-2/Ig protein also augmented the **vaccine**-elicited immune responses, but less effectively than IL-2/Ig **plasmid**. Augmentation of the immune responses by IL-2/Ig was evident after the primary immunization and increased with subsequent boost immunizations. These results demonstrate that the administration of IL-2/Ig **plasmid** can substantially augment **vaccine**-elicited humoral and cellular immune responses in higher primates.

L60 ANSWER 16 OF 22 MEDLINE on STN

1999345234. PubMed ID: 10418893. Xenogeneic and allogeneic anti-MHC immune responses induced by **plasmid** DNA immunization. Dela Cruz C S; Chamberlain J W; MacDonald K S; Barber B H. (Institute of Medical Sciences, University of Toronto, Ontario, Canada.) Vaccine, (1999 Jun 4) 17 (20-21) 2479-92. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Major histocompatibility complex (MHC) proteins are known to be incorporated into the human immunodeficiency virus (HIV-1) envelope as the virion buds from the host cell surface. Studies using **simian immunodeficiency virus** (**SIV**) infection of macaques have demonstrated that immunization with uninfected human cells or purified HLA proteins can provide protection from challenge with live **SIV** when it is grown in human cells expressing the same MHC alleles. Thus the induction of anti-MHC immune responses represents an important option to consider with respect to **vaccine** design for **SIV** and HIV. Here we examine **plasmid** DNA immunization strategies as an alternative to cellular or protein immunogens for the induction of xenogeneic and allogeneic immune responses in C57BL/6 mice and in an HLA transgenic mouse model system, respectively. We compared the immunogenicity of HLA-A2- and HLA-B27-expressing splenocytes with the corresponding **plasmid** DNA immunogens. Results from the transgenic mouse experiments indicate that **plasmid** DNA immunization with both **class I** and class II MHC-encoding vectors can elicit antibody responses recognizing conformationally intact MHC molecules. Our data also show that immunization with **class I** MHC-encoding DNA immunogens can elicit **cytotoxic** T-lymphocyte responses, demonstrating the potential to mobilize both antibody and cell-mediated anti-MHC immune responses in the context of this approach to HIV-1 **vaccine** design.

L60 ANSWER 17 OF 22 MEDLINE on STN

1999217703. PubMed ID: 10203053. Protection from pathogenic **SIV** challenge using multigenic DNA **vaccines**. Haigwood N L; Pierce C C; Robertson M N; Watson A J; Montefiori D C; Rabin M; Lynch J B; Kuller L; Thompson J; Morton W R; Benveniste R E; Hu S L; Greenberg P; Mossman S P.

haigwood@u.washington.edu) . Immunology letters, (1999 Mar) 66 (1-3) 183-8. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB To assess DNA immunization as a strategy for protecting against HIV infection in humans, we utilized SIVmne infection of Macaca fascicularis as a **vaccine** challenge model with moderate pathogenic potential. We compared the efficacy of DNA immunization alone and in combination with subunit protein boosts. All of the structural and regulatory genes of SIVmne clone 8 were cloned into mammalian expression vectors under the control of the CMV IE-1 promoter. Eight M. fascicularis were immunized twice with 3 mg of **plasmid** DNA divided between two sites; intramuscular and intradermal. Four primed macaques received a further two DNA immunizations at weeks 16-36, while the second group of four were boosted with 250 microg recombinant gp160 plus 250 microg recombinant Gag-Pol particles formulated in MF-59 adjuvant. Half of the controls received four immunizations of vector DNA; half received two vector DNA and two adjuvant immunizations. As expected, humoral immune responses were stronger in the macaques receiving subunit boosts, but responses were sustained in both groups. Significant neutralizing antibody titers to SIVmne were detected in one of the subunit-boosted animals and in none of the DNA-only animals prior to challenge. T-cell proliferative responses to gp160 and to Gag were detected in all immunized animals after three immunizations, and these responses increased after four immunizations. Cytokine profiles in PHA-stimulated PBMC taken on the day of challenge showed trends toward Th1 responses in 2/4 macaques in the DNA **vaccinated** group and in 1/4 of the DNA plus subunit **vaccinated** macaques; Th2 responses in 3/4 DNA plus subunit-immunized macaques; and Th0 responses in 4/4 controls. In bulk **CTL** culture, **SIV** specific lysis was low or undetectable, even after four immunizations. However, stable **SIV** Gag-Pol- and env-specific T-cell clones (CD3+ CD8+) were isolated after only two DNA immunizations, and Gag-Pol- and Nef-specific **CTL** lines were isolated on the day of challenge. All animals were challenged at week 38 with SIVmne uncloned stock by the intrarectal route. Based on antibody anamnestic responses (western, ELISA, and neutralizing antibodies) and virus detection methods (co-culture of PBMC and LNMC, nested set PCR- of DNA from PBMC and LNMC, and plasma QC-PCR), there were major differences between the groups in the challenge outcome. Surprisingly, sustained low virus loads were observed only in the DNA group, suggesting that four immunizations with DNA only elicited more effective immune responses than two DNA primes combined with two protein boosts. Multigenic DNA **vaccines** such as these, bearing all structural and regulatory genes, show significant promise and may be a safe alternative to live-attenuated **vaccines**.

L60 ANSWER 18 OF 22 MEDLINE on STN

1999217702. PubMed ID: 10203052. Pre-clinical development of a multi-**CTL** epitope-based DNA prime MVA boost **vaccine** for AIDS. Hanke T; McMichael A. (Institute of Molecular Medicine, University of Oxford, The John Radcliffe Hospital, UK.. hanke@molbiol.ox.ac.uk) . Immunology letters, (1999 Mar) 66 (1-3) 177-81. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB Reliable and effective methods for induction of **cytotoxic** T-lymphocytes (**CTL**) are constantly persued. Central to this search is work in animal models, which allow to test novel **vaccine** strategies and ultimately lead to a more efficient planning of clinical trials. Here, human immunodeficiency virus (HIV) **vaccine** candidates were constructed as a string of partially overlapping **CTL** epitopes (20 human, 3 macaque and 1 mouse) delivered and expressed using **plasmid** DNA and modified virus Ankara (MVA; an attenuated **vaccinia** virus), which are both **vaccine** vehicles acceptable for use in humans. In mice, these **vaccines** were shown to induce virus-specific interferon-gamma-producing and cytolytic CD8+ T-cells after a single intramuscular needle injection. When immunization protocols were sought which would improve the level of induced HIV-specific T-cells, DNA priming-MVA boosting was found to be the most potent protocol. The multi-epitope DNA also elicited **CTL** when

Finally, a combined intradermal gene gun DNA-MVA **vaccination** regimen induced in macaques high frequencies of circulating **CTL**, which were comparable to those observed in **simian immunodeficiency virus** (**SIV**)-infected monkeys. Further optimization of this method in non-human primates is under way. Thus, a **vaccination** regimen for an effective elicitation of **CTL** has been developed which might facilitate evaluation of the role(s) that these lymphocytes play in the control of **SIV** and HIV infections.

L60 ANSWER 19 OF 22 MEDLINE on STN
1998435937. PubMed ID: 9764908. Replication-defective HIV as a **vaccine** candidate. Tung F Y; Rinaldo C R Jr; Montelaro R C. (Department of Infectious Disease and Microbiology, University of Pittsburgh, Pennsylvania 15261, USA.) AIDS research and human retroviruses, (1998 Sep 20) 14 (14) 1247-52. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Live attenuated **vaccines** prepared from **simian immunodeficiency virus** (**SIV**) have provided the best protective immunity in challenge experiments. In animals **vaccinated** with attenuated **SIV**, immune responses may be elicited owing to endogenous expression of native **SIV** proteins and/or antigen presentation in the native replication site of virus. However, replication-competent viral **vaccines** raise safety concerns for clinical trials in humans. To ensure the safety and maintain the immunogenicity of a live, attenuated **vaccine**, we have developed a replication-defective HIV pseudotyped with vesicular stomatitis virus G protein (VSV-G). The polymerase gene of HIV was truncated to construct the replication-defective HIV. This pseudotyped HIV can infect many cell types, including human and simian cells, and undergoes only one round of replication. Furthermore, antibody immune response can be detected in mice immunized with VSV-G-pseudotyped replication-defective HIV.

L60 ANSWER 20 OF 22 MEDLINE on STN
1998222345. PubMed ID: 9561560. Study of the immunogenicity of different recombinant Mengo viruses expressing HIV1 and **SIV** epitopes. Van der Ryst E; Nakasone T; Habel A; Venet A; Gomard E; Altmeyer R; Girard M; Borman A M. (Unite de Virologie moleculaire, Institut Pasteur, Paris.) Research in virology, (1998 Jan-Feb) 149 (1) 5-20. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB Recombinant Mengo viruses expressing heterologous genes have proven to be safe and immunogenic in both mice and primates, and to be able to induce both humoral and cellular immune responses (Altmeyer et al., 1995, 1996). Several recombinant Mengo viruses expressing either a large region (aa 65-206) of the HIV1 nef gene product, or **cytotoxic** T lymphocyte (**CTL**) epitopic regions from the **SIV** Gag (aa 182-190), Nef (aa 155-178) and Pol (aa 587-601) gene products were engineered. The heterologous antigens were expressed either as fusion proteins with the Mengo virus leader (L) protein, or in cleaved form through autocatalytic cleavage by the foot-and-mouth disease virus 2A protein. Rhesus macaques and BALB/c mice inoculated with the Mengo virus **SIV** recombinants failed to develop **CTL** responses against the **SIV** gene products, while one of the HIV-Nef recombinants induced a weak **CTL** response in mice directed to an HIV1 Nef peptide spanning positions 182-198. In contrast, BALB/c mice immunized with **vaccinia** virus recombinants expressing HIV1 Nef developed a strong **CTL** response to the 182-198 peptide and also responded to a second peptide spanning positions 73-81. These results indicate that Mengo virus recombinants expressing HIV1 Nef and **SIV CTL** epitopes are weak immunogens. One of the fusion recombinants expressing **SIV CTL** epitopes failed to infect macaques even when used at high doses, while the recombinant expressing HIV1 Nef as a fusion protein failed to infect BALB/c mice. These results demonstrate that the expression of certain heterologous sequences as fusion proteins with L can result in the loss of the ability of the recombinant to infect normally susceptible animals.

L60 ANSWER 21 OF 22 MEDLINE on STN
97047126. PubMed ID: 8892046. In vivo protective anti-HIV immune responses

E; Agadjanyan M; Javadian A; Frost P; Dang K; Carrano R A; Ciccarelli R; Coney L; Williams W V; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Journal of medical primatology, (1996 Jun) 25 (3) 242-50. Journal code: 0320626. ISSN: 0047-2565. Pub. country: Denmark. Language: English.

AB An effective immune response involves the specific recognition of and elimination of an infectious organism at multiple levels. In this context DNA immunization can present functional antigenic proteins to the host for recognition by all arms of the immune system, yet provides the opportunity to delete any genes of the infectious organism which code for antigens or pieces of antigens that may have deleterious effects. Our group has developed the use of nucleic acid immunization as a possible method of **vaccination** against Human immunodeficiency virus type 1 (HIV-1) [1,2,3,10,11,12]. Sera from non-human primates immunized with DNA vectors that express the envelope proteins from HIV-1 contain antibodies specific to the HIV-1 envelope. These sera also neutralize HIV-1 infection in vitro and inhibit cell to cell infection in tissue culture. Analysis of cellular responses is equally encouraging. T cell proliferation as well as **cytotoxic** T cell lysis of relevant env expressing target cells were observed. In addition, evidence that DNA **vaccines** are capable of inducing a protective response against live virus was demonstrated using a chimeric **SIV**/HIV (SHIV) challenge in **vaccinated** cynomologous macaques. We found that nucleic acid **vaccination** induced protection from challenge in one out of four immunized cynomolgus macaques and viral load was lower in the **vaccinated** group of animals versus the control group of animals. These data encouraged us to analyze this **vaccination** technique in chimpanzees, the most closely related animal species to man. We observed the induction of both cellular and humoral immune responses with a DNA **vaccine** in chimpanzees. These studies demonstrate the utility of this technology to induce relevant immune responses in primates which may ultimately lead to effective **vaccines**.

L60 ANSWER 22 OF 22 MEDLINE on STN
96099492. PubMed ID: 8523593. **Simian immunodeficiency virus**-specific **cytotoxic** T-lymphocyte induction through DNA **vaccination** of rhesus monkeys. Yasutomi Y; Robinson H L; Lu S; Mustafa F; Lekutis C; Arthos J; Mullins J I; Voss G; Manson K; Wyand M; Letvin N L. (Division of Viral Pathogenesis, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA.) Journal of virology, (1996 Jan) 70 (1) 678-81. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In view of the growing evidence that virus-specific **cytotoxic** T lymphocytes (**CTL**) play an important role in containing the early spread of human immunodeficiency virus type 1 (HIV-1) in infected individuals, novel **vaccine** strategies capable of eliciting HIV-1-specific **CTL** are being pursued in attempts to create an effective AIDS **vaccine**. We have used the **simian immunodeficiency virus** of macaques (SIVmac)/rhesus monkey model to explore the induction of AIDS virus-specific **CTL** responses by DNA **vaccination**. We found that the inoculation of rhesus monkeys with **plasmid** DNA encoding SIVmac Env and Gag elicited a persisting SIVmac-specific memory **CTL** response. These **CTL** were CD8+ and major histocompatibility complex **class I** restricted. These studies provide evidence for the potential utility of DNA inoculation as an approach to an HIV-1 **vaccine**.

=> d his

(FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
E SCHWARTZ OLIVIER/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

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     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
L24           1 S E2
L25           0 S L24 NOT L20
                E RIVIERE Y/AU
L26         104 S E3 OR E4
L27         101 S L26 NOT L20
                E HEARD J M/AU
L28           7 S E8
L29           7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30        2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31        1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32         795 S L31 AND EXOGENOUS
L33         790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34          77 S L33 AND PLASMID/CLM
L35          11 S L34 AND PY<2002
L36          49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37         138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38          10 S L37 AND DENDRITIC
L39           1 S L38 AND (GENE VACCINATION)
L40         181 S (NAKED PLASMID DNA)
L41          11 S L40 AND PY=1996
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L43          0 S L40 AND (MULTIVALENT)
L44         80 S MULTIVALENT VACCINE
L45          1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46        162 S MULTIVALEN? VACCIN?
L47          6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48          0 S L46 AND (TWO PLASMIDS)
L49          1 S (MULTI-PLASMID DNA VACCINATION)
L50     140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51       7795 S L50 AND VACCIN?
L52        324 S L51 AND (PLASMID?)
L53        324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54        132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55       4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56       1102 S L55 AND VACCIN?
L57         70 S L56 AND PLASMID?
L58         25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59          3 S L58 NOT L54
L60         22 S L58 NOT L59

=>
=> s (in vivo gene delivery)
        349461 VIVO
        679819 GENE
        165200 DELIVERY
L61        203 (IN VIVO GENE DELIVERY)
                 (VIVO(W)GENE(W)DELIVERY)

=> s l61 and (stable transduction)
        166683 STABLE
        120160 TRANSDUCTION
            72 STABLE TRANSDUCTION
                 (STABLE(W)TRANSDUCTION)
L62          1 L61 AND (STABLE TRANSDUCTION)

=> d l62,cbib,ab
```

L62 ANSWER 1 OF 1 MEDLINE on STN
96181116. PubMed ID: 8602510. In **vivo gene delivery** and **stable transduction** of nondividing cells by a lentiviral vector. Naldini L; Blomer U; Gallay P; Ory D; Mulligan R; Gage F H; Verma I M; Trono D. (Salk Institute, La Jolla, CA 92037, USA.) Science, (1996 Apr 12) 272 (5259) 263-7. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB A retroviral vector system based on the human immunodeficiency virus (HIV) was developed that, in contrast to a murine leukemia virus-based counterpart, transduced heterologous sequences into HeLa cells and rat fibroblasts blocked in the cell cycle, as well as into human primary macrophages. Additionally, the HIV vector could mediate stable in vivo gene transfer into terminally differentiated neurons. The ability of HIV-based viral vectors to deliver genes in vivo into nondividing cells could increase the applicability of retroviral vectors in human gene therapy.

```
=> e whitt m a/au
E1           1      WHITT L A/AU
E2           4      WHITT M/AU
E3          25 --> WHITT M A/AU
E4           3      WHITT M C/AU
E5           1      WHITT MELICIA/AU
E6           3      WHITT MELICIA C/AU
E7           6      WHITT MICHAEL A/AU
E8           1      WHITT N A/AU
E9           2      WHITT P/AU
E10          3      WHITT P B/AU
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E12           1     WHITT R/AU

=> s e3
L63          25 "WHITT M A"/AU

=> s l63 and py=1990
         388037 PY=1990
L64           1 L63 AND PY=1990

=> d l64,cbib,ab,

L64  ANSWER 1 OF 1     MEDLINE on STN
90376446.    PubMed ID: 2168975.   A fusion-defective mutant of the vesicular
     stomatitis virus glycoprotein. Whitt M A; Zagouras P; Crise B; Rose J K.
     (Department of Pathology, Yale University School of Medicine, New Haven,
     Connecticut 06510. ) Journal of virology, (1990 Oct) 64 (10) 4907-13.
     Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States.
     Language: English.
AB   We have recently described an assay in which a temperature-sensitive
     mutant of vesicular stomatitis virus (VSV; mutant ts045), encoding a
     glycoprotein that is not transported to the cell surface, can be rescued
     by expression of wild-type VSV glycoproteins from cDNA (M.  Whitt, L.
     Chong, and J.  Rose, J.  Virol. 63:3569-3578, 1989).  Here we examined the
     ability of mutant G proteins to rescue ts045.  We found that one mutant
     protein (QN-1) having an additional N-linked oligosaccharide at amino acid
     117 in the extracellular domain was incorporated into VSV virions but that
     the virions containing this glycoprotein were not infectious.  Further
     analysis showed that virus particles containing the mutant protein would
     bind to cells and were endocytosed with kinetics identical to those of
     virions rescued with wild-type G protein.  We also found that QN-1 lacked
     the normal membrane fusion activity characteristic of wild-type G protein.
     The absence of fusion activity appears to explain lack of particle
     infectivity.  The proximity of the new glycosylation site to a sequence of
     19 uncharged amino acids (residues 118 to 136) that is conserved in the
     glycoproteins of the two VSV serotypes suggests that this region may be
     involved in membrane fusion.  The mutant glycoprotein also interferes
     strongly with rescue of virus by wild-type G protein.  The strong
     interference may result from formation of heterotrimers that lack fusion
     activity.


=> e amara r r/au
E1            1     AMARA PATRICIA/AU
E2            3     AMARA R/AU
E3            7 --> AMARA R R/AU
E4            1     AMARA RAMA R/AU
E5           10     AMARA RAMA RAO/AU
E6            7     AMARA S/AU
E7           84     AMARA S G/AU
E8            1     AMARA S V/AU
E9            1     AMARA SANDRINE/AU
E10           1     AMARA SREENIVASRAO/AU
E11           8     AMARA SUSAN G/AU
E12           1     AMARA T/AU

=> s e3
L65           7 "AMARA R R"/AU

=> s l65 and py=2001
         515029 PY=2001
L66           2 L65 AND PY=2001

=> d l66,cbib,ab,1-2

L66  ANSWER 1 OF 2     MEDLINE on STN
```

DNA-raised immune responses by mutant caspases. Sasaki S; **Amara R R**; Oran A E; Smith J M; Robinson H L. (Division of Microbiology and Immunology, Yerkes Regional Primate Research Center of Emory University, Atlanta, GA 30329, USA.) Nature biotechnology, **(2001 Jun)** 19 (6) 543-7. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB Apoptotic bodies can be used to target delivery of DNA-expressed immunogens into professional antigen-presenting cells (APCs). Here we show that antigen-laden apoptotic bodies created by vectors co-expressing influenza virus hemagglutinin (HA) or nucleoprotein (NP) genes and mutant caspase genes markedly increased T-cell responses. Both CD8 and CD4 T-cell responses were affected. The adjuvant activity was restricted to partially inactivated caspases that allowed immunogen expression before the generation of apoptotic bodies. Active-site mutants of murine caspase 2 and an autocatalytic chimera of murine caspase 2 prodomain and human caspase 3 induced apoptosis that did not interfere with immunogen expression. The adjuvant activity also enhanced B-cell responses, but to a lesser extent than T-cell responses. The large increases in T-cell responses represent one of the strongest effects to date of a DNA adjuvant on cellular immunity.

L66 ANSWER 2 OF 2 MEDLINE on STN

2001316872. PubMed ID: 11393868. Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. **Amara R R**; Villinger F; Altman J D; Lydy S L; O'Neil S P; Staprans S I; Montefiori D C; Xu Y; Herndon J G; Wyatt L S; Candido M A; Kozyr N L; Earl P L; Smith J M; Ma H L; Grimm B D; Hulsey M L; Miller J; McClure H M; McNicholl J M; Moss B; Robinson H L. (Vaccine Research Center and Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30329, USA.) Science, **(2001 Apr 6)** 292 (5514) 69-74. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Heterologous prime/boost regimens have the potential for raising high levels of immune responses. Here we report that DNA priming followed by a recombinant modified vaccinia Ankara (rMVA) booster controlled a highly pathogenic immunodeficiency virus challenge in a rhesus macaque model. Both the DNA and rMVA components of the vaccine expressed multiple immunodeficiency virus proteins. Two DNA inoculations at 0 and 8 weeks and a single rMVA booster at 24 weeks effectively controlled an intrarectal challenge administered 7 months after the booster. These findings provide hope that a relatively simple multiprotein DNA/MVA vaccine can help to control the acquired immune deficiency syndrome epidemic.

```
=> e buseyne f/au
E1            3      BUSEY W/AU
E2           22      BUSEY W M/AU
E3           22 --> BUSEYNE F/AU
E4            3      BUSEYNE FLORENCE/AU
E5            3      BUSFIELD B L JR/AU
E6           16      BUSFIELD D/AU
E7           10      BUSFIELD F/AU
E8            2      BUSFIELD FRANCES/AU
E9            1      BUSFIELD G/AU
E10           5      BUSFIELD J/AU
E11           2      BUSFIELD JOAN/AU
E12           3      BUSFIELD P I/AU

=> s e3
L67          22 "BUSEYNE F"/AU

=> s l67 and py=2001
         515029 PY=2001
L68           6 L67 AND PY=2001
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11390 VIRION
L69 2 L68 AND VIRION

=> d l69,cbib,ab,1-2

L69 ANSWER 1 OF 2 MEDLINE on STN
2001397911. PubMed ID: 11448175. Nef is required for efficient HIV-1 replication in cocultures of dendritic cells and lymphocytes. Petit C; **Buseyne F**; Boccaccio C; Abastado J P; Heard J M; Schwartz O. (Unite Retrovirus et Transfert Genetique, Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, 28 rue du Dr Roux, Paris Cedex 15, 75724, France.) Virology, **(2001 Jul 20)** 286 (1) 225-36. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) are thought to play a crucial role in the pathogenesis of HIV-1 infection. DCs are believed to transport virus particles to lymph nodes before transfer to CD4(+) lymphocytes. We have investigated the role of Nef in these processes. HIV-1 replication was examined in human immature DC-lymphocyte cocultures and in DCs or lymphocytes separately. Using various R5-tropic and X4-tropic HIV-1 strains and their nef-deleted (Deltanef) counterparts, we show that Nef is required for optimal viral replication in immature DC-T cells clusters and in T lymphocytes. Nef exerts only a marginal role on viral replication in immature DCs alone as well as on **virion** capture by DCs, long-term intracellular accumulation and transmission of X4 strains to lymphocytes. We also show that wild-type and Deltanef virions are similarly processed for MHC-I restricted exogenous presentation by DCs. Taken together, these results help explain how HIV-1 Nef may affect viral spread and immune responses in the infected host.
Copyright 2001 Academic Press.

L69 ANSWER 2 OF 2 MEDLINE on STN
2001198778. PubMed ID: 11231634. MHC-I-restricted presentation of HIV-1 **virion** antigens without viral replication. **Buseyne F**; Le Gall S; Boccaccio C; Abastado J P; Lifson J D; Arthur L O; Riviere Y; Heard J M; Schwartz O. (Laboratoire d'Immunopathologie Viralem, Institut Pasteur, Paris, France.) Nature medicine, **(2001 Mar)** 7 (3) 344-9. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Dendritic cells and macrophages can process extracellular antigens for presentation by MHC-I molecules. This exogenous pathway may have a crucial role in the activation of CD8+ cytotoxic T lymphocytes during human viral infections. We show here that HIV-1 epitopes derived from incoming virions are presented through the exogenous MHC-I pathway in primary human dendritic cells, and to a lower extent in macrophages, leading to cytotoxic T-lymphocyte activation in the absence of viral protein synthesis. Exogenous antigen presentation required adequate virus-receptor interactions and fusion of viral and cellular membranes. These results provide new insights into how anti-HIV cytotoxic T lymphocytes can be activated and have implications for anti-HIV vaccine design.

=> d his

(FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
E SCHWARTZ OLIVIER/IN
L1 2 S E3

FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
E BUSEYNE FLORENCE/IN
L2 1 S E3
L3 0 S L2 NOT L1

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L4             1 S E3
L5             0 S L4 NOT L1
                 E RIVIERE YVES/IN
L6             2 S E3
L7             1 S L6 NOT L1
                 E HEARD JEAN MICHEL/IN
L8             6 S E3
L9             5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                 E SCHWARTZ OLIVIER/IN
                 E SCHWARTZ O/IN
L10           16 S E3-E5
                 E BUSEYNE F/IN
L11            1 S E3
L12            0 S L11 NOT L10
                 E MARSAC D/IN
L13            2 S E3
L14            1 S L13 NOT L10
                 E RIVIERE Y/IN
L15            7 S E3 OR E4
L16            6 S L15 NOT L10
                 E HEARD J/IN
L17            2 S E8
L18            2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                 E SCHWARTZ O/AU
L19           10 S E7
L20           90 S E3
L21            2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                 E BUSEYNE F/AU
L22           25 S E3 OR E4
L23           21 S L22 NOT L20
                 E MARSAC E/AU
L24            1 S E2
L25            0 S L24 NOT L20
                 E RIVIERE Y/AU
L26          104 S E3 OR E4
L27          101 S L26 NOT L20
                 E HEARD J M/AU
L28            7 S E8
L29            7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                 E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30         2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31         1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32          795 S L31 AND EXOGENOUS
L33          790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34           77 S L33 AND PLASMID/CLM
L35           11 S L34 AND PY<2002
L36           49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37          138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38           10 S L37 AND DENDRITIC
L39            1 S L38 AND (GENE VACCINATION)
L40          181 S (NAKED PLASMID DNA)
L41           11 S L40 AND PY=1996
L42            5 S L40 AND DENDRITIC
L43            0 S L40 AND (MULTIVALENT)
L44           80 S MULTIVALENT VACCINE
L45            1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46          162 S MULTIVALEN? VACCIN?
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L48              0 S L46 AND (TWO PLASMIDS)
L49              1 S (MULTI-PLASMID DNA VACCINATION)
L50         140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51           7795 S L50 AND VACCIN?
L52            324 S L51 AND (PLASMID?)
L53            324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54            132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55           4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56           1102 S L55 AND VACCIN?
L57             70 S L56 AND PLASMID?
L58             25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59              3 S L58 NOT L54
L60             22 S L58 NOT L59
L61            203 S (IN VIVO GENE DELIVERY)
L62              1 S L61 AND (STABLE TRANSDUCTION)
                   E WHITT M A/AU
L63             25 S E3
L64              1 S L63 AND PY=1990
                   E AMARA R R/AU
L65              7 S E3
L66              2 S L65 AND PY=2001
                   E BUSEYNE F/AU
L67             22 S E3
L68              6 S L67 AND PY=2001
L69              2 S L68 AND VIRION

=> e naldini l/au
E1             1      NALDINI E/AU
E2            22      NALDINI G/AU
E3            60 -->  NALDINI L/AU
E4            18      NALDINI LUIGI/AU
E5             2      NALDJIAN S/AU
E6             9      NALDO J/AU
E7             9      NALDO J L/AU
E8             1      NALDO JESUS L/AU
E9            11      NALDOKEN S/AU
E10            4      NALDOKEN SENIHA/AU
E11            5      NALDONI A/AU
E12           21      NALDONI C/AU

=> s e3
L70           60 "NALDINI L"/AU

=> s l70 and py=1996
        422579 PY=1996
L71            3 L70 AND PY=1996

=> d l71,ti,1-3

L71  ANSWER 1 OF 3     MEDLINE on STN
TI   Efficient transfer, integration, and sustained long-term expression of the
     transgene in adult rat brains injected with a lentiviral vector.

L71  ANSWER 2 OF 3     MEDLINE on STN
TI   Applications of gene therapy to the CNS.

L71  ANSWER 3 OF 3     MEDLINE on STN
TI   In vivo gene delivery and stable transduction of nondividing cells by a
     lentiviral vector.


=> d l71,cbib,ab,3

L71  ANSWER 3 OF 3     MEDLINE on STN
96181116.    PubMed ID: 8602510.   In vivo gene delivery and stable
```

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    Blomer U; Gallay P; Ory D; Mulligan R; Gage F H; Verma I M; Trono D. (Salk
    Institute, La Jolla, CA 92037, USA. ) Science, (1996 Apr 12) 272 (5259)
    263-7. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United
    States. Language: English.
AB  A retroviral vector system based on the human immunodeficiency virus (HIV)
    was developed that, in contrast to a murine leukemia virus-based
    counterpart, transduced heterologous sequences into HeLa cells and rat
    fibroblasts blocked in the cell cycle, as well as into human primary
    macrophages. Additionally, the HIV vector could mediate stable in vivo
    gene transfer into terminally differentiated neurons. The ability of
    HIV-based viral vectors to deliver genes in vivo into nondividing cells
    could increase the applicability of retroviral vectors in human gene
    therapy.


=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
L17           2 S E8
L18           2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                E SCHWARTZ O/AU
L19          10 S E7
L20          90 S E3
L21           2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                E BUSEYNE F/AU
L22          25 S E3 OR E4
L23          21 S L22 NOT L20
                E MARSAC E/AU
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```
L25             0 S L24 NOT L20
                  E RIVIERE Y/AU
L26           104 S E3 OR E4
L27           101 S L26 NOT L20
                  E HEARD J M/AU
L28             7 S E8
L29             7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                  E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30          2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31          1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32           795 S L31 AND EXOGENOUS
L33           790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34            77 S L33 AND PLASMID/CLM
L35            11 S L34 AND PY<2002
L36            49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37           138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38            10 S L37 AND DENDRITIC
L39             1 S L38 AND (GENE VACCINATION)
L40           181 S (NAKED PLASMID DNA)
L41            11 S L40 AND PY=1996
L42             5 S L40 AND DENDRITIC
L43             0 S L40 AND (MULTIVALENT)
L44            80 S MULTIVALENT VACCINE
L45             1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46           162 S MULTIVALEN? VACCIN?
L47             6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48             0 S L46 AND (TWO PLASMIDS)
L49             1 S (MULTI-PLASMID DNA VACCINATION)
L50        140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51          7795 S L50 AND VACCIN?
L52           324 S L51 AND (PLASMID?)
L53           324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54           132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55          4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56          1102 S L55 AND VACCIN?
L57            70 S L56 AND PLASMID?
L58            25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59             3 S L58 NOT L54
L60            22 S L58 NOT L59
L61           203 S (IN VIVO GENE DELIVERY)
L62             1 S L61 AND (STABLE TRANSDUCTION)
                  E WHITT M A/AU
L63            25 S E3
L64             1 S L63 AND PY=1990
                  E AMARA R R/AU
L65             7 S E3
L66             2 S L65 AND PY=2001
                  E BUSEYNE F/AU
L67            22 S E3
L68             6 S L67 AND PY=2001
L69             2 S L68 AND VIRION
                  E NALDINI L/AU
L70            60 S E3
L71             3 S L70 AND PY=1996

=> s l70 and py=1997
        431893 PY=1997
L72             2 L70 AND PY=1997

=> d l72,ti,1-2
```

L72 ANSWER 1 OF 2 MEDLINE on STN

TI Multiply attenuated lentiviral vector achieves efficient gene delivery in vivo.

L72 ANSWER 2 OF 2 MEDLINE on STN

TI Highly efficient and sustained gene transfer in adult neurons with a lentivirus vector.

=> d l72,cbib,ab,1-2

L72 ANSWER 1 OF 2 MEDLINE on STN

97451449. PubMed ID: 9306402. Multiply attenuated lentiviral vector achieves efficient gene delivery in vivo. Zufferey R; Nagy D; Mandel R J; **Naldini L**; Trono D. (Salk Institute, La Jolla, CA 92037-1099, USA.) Nature biotechnology, **(1997 Sep)** 15 (9) 871-5. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB Retroviral vectors derived from lentiviruses such as HIV-1 are promising tools for human gene therapy because they mediate the in vivo delivery and long-term expression of transgenes in nondividing tissues. We describe an HIV vector system in which the virulence genes env, vif, vpr, vpu, and nef have been deleted. This multiply attenuated vector conserved the ability to transduce growth-arrested cells and monocyte-derived macrophages in culture, and could efficiently deliver genes in vivo into adult neurons. These data demonstrate the potential of lentiviral vectors in human gene therapy.

L72 ANSWER 2 OF 2 MEDLINE on STN

97404674. PubMed ID: 9261386. Highly efficient and sustained gene transfer in adult neurons with a lentivirus vector. Blomer U; **Naldini L**; Kafri T; Trono D; Verma I M; Gage F H. (Salk Institute for Biological Studies, La Jolla, California 92037, USA.) Journal of virology, **(1997 Sep)** 71 (9) 6641-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The identification of monogenic and complex genes responsible for neurological disorders requires new approaches for delivering therapeutic protein genes to significant numbers of cells in the central nervous system. A lentivirus-based vector capable of infecting dividing and quiescent cells was investigated in vivo by injecting highly concentrated viral vector stock into the striatum and hippocampus of adult rats. Control brains were injected with a Moloney murine leukemia virus, adenovirus, or adeno-associated virus vector. The volumes of the areas containing transduced cells and the transduced-cell densities were stereologically determined to provide a basis for comparison among different viral vectors and variants of the viral vector stocks. The efficiency of infection by the lentivirus vector was improved by deoxynucleoside triphosphate pretreatment of the vector and was reduced following mutation of integrase and the Vpr-matrix protein complex involved in the nuclear translocation of the preintegration complex. The lentivirus vector system was able to efficiently and stably infect quiescent cells in the primary injection site with transgene expression for over 6 months. Triple labeling showed that 88.7% of striatal cells transduced by the lentivirus vector were terminally differentiated neurons.

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=> e rock k l/au
E1            7      ROCK K/AU
E2            3      ROCK K C/AU
E3          112 -->  ROCK K L/AU
E4            1      ROCK K M/AU
E5            1      ROCK KELLEE A/AU
E6            1      ROCK KENNETH/AU
E7           10      ROCK KENNETH L/AU
E8            1      ROCK KRESS D/AU
E9            2      ROCK KRESS DIANE/AU
```

E11 4 ROCK L/AU
E12 1 ROCK L A/AU

=> s e3
L73 112 "ROCK K L"/AU

=> s l73 and py=1996
422579 PY=1996
L74 7 L73 AND PY=1996

=> d l74,ti,1-7

L74 ANSWER 1 OF 7 MEDLINE on STN
TI Major histocompatibility class I presentation of soluble antigen facilitated by Mycobacterium tuberculosis infection.

L74 ANSWER 2 OF 7 MEDLINE on STN
TI A new foreign policy: MHC class I molecules monitor the outside world.

L74 ANSWER 3 OF 7 MEDLINE on STN
TI Antigen processing and presentation by the class I major histocompatibility complex.

L74 ANSWER 4 OF 7 MEDLINE on STN
TI Proteasome subunits X and Y alter peptidase activities in opposite ways to the interferon-gamma-induced subunits LMP2 and LMP7.

L74 ANSWER 5 OF 7 MEDLINE on STN
TI Chemical denaturation and modification of ovalbumin alters its dependence on ubiquitin conjugation for class I antigen presentation.

L74 ANSWER 6 OF 7 MEDLINE on STN
TI Analysis of the role of MHC class II presentation in the stimulation of cytotoxic T lymphocytes by antigens targeted into the exogenous antigen-MHC class I presentation pathway.

L74 ANSWER 7 OF 7 MEDLINE on STN
TI Analysis of MHC class II presentation of particulate antigens of B lymphocytes.

=> d l74,cbib,ab,1-3

L74 ANSWER 1 OF 7 MEDLINE on STN
97030274. PubMed ID: 8876215. Major histocompatibility class I presentation of soluble antigen facilitated by Mycobacterium tuberculosis infection. Mazzaccaro R J; Gedde M; Jensen E R; van Santen H M; Ploegh H L; **Rock K L**; Bloom B R. (Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461, USA.) Proceedings of the National Academy of Sciences of the United States of America, **(1996 Oct 15)** 93 (21) 11786-91. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB Cell-mediated immune responses are essential for protection against many intracellular pathogens. For Mycobacterium tuberculosis (MTB), protection requires the activity of T cells that recognize antigens presented in the context of both major histocompatibility complex (MHC) class II and I molecules. Since MHC class I presentation generally requires antigen to be localized to the cytoplasmic compartment of antigen-presenting cells, it remains unclear how pathogens that reside primarily within endocytic vesicles of infected macrophages, such as MTB, can elicit specific MHC class I-restricted T cells. A mechanism is described for virulent MTB that allows soluble antigens ordinarily unable to enter the cytoplasm, such as ovalbumin, to be presented through the MHC class I pathway to T cells. The mechanism is selective for MHC class I presentation, since MTB infection inhibited MHC class II presentation of ovalbumin. The MHC class

dependent upon the transporter associated with antigen processing (TAP), which translocates antigenic peptides from the cytoplasm into the endoplasmic reticulum. The process is mimicked by Listeria monocytogenes and soluble listeriolysin, a pore-forming hemolysin derived from it, suggesting that virulent MTB may have evolved a comparable mechanism that allows molecules in a vacuolar compartment to enter the cytoplasmic presentation pathway for the generation of protective MHC class I-restricted T cells.

L74 ANSWER 2 OF 7 MEDLINE on STN
96417480. PubMed ID: 8820271. A new foreign policy: MHC class I molecules monitor the outside world. **Rock K L.** (Division of Lymphocyte Biology, Dana Farber Cancer Institute, Boston, MA 02115, USA.. Kenneth_Rock@dfci.harvard.edu) . Immunology today, **(1996 Mar)** 17 (3) 131-7. Ref: 56. Journal code: 8008346. ISSN: 0167-5699. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Although most cells exclusively use their major histocompatibility complex (MHC) class I molecules to present peptides from endogenous proteins, phagocytes also use them to present exogenous antigens. Here, Kenneth Rock describes how this novel antigen-presenting pathway may play an important role in immune surveillance for intracellular bacteria or parasites, as well as for viral infections and tumors affecting somatic tissues.

L74 ANSWER 3 OF 7 MEDLINE on STN
96292433. PubMed ID: 8717519. Antigen processing and presentation by the class I major histocompatibility complex. York I A; **Rock K L.** (Department of Lymphocyte Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.) Annual review of immunology, **(1996)** 14 369-96. Ref: 187. Journal code: 8309206. ISSN: 0732-0582. Pub. country: United States. Language: English.

AB Major histocompatibility complex (MHC) class I molecules bind peptides derived from cellular proteins and display them for surveillance by the immune system. These peptide-binding molecules are composed of a heavy chain, containing an antigen-binding groove, which is tightly associated with a light chain (beta 2-microglobulin). The majority of presented peptides are generated by degradation of proteins in the cytoplasm, in many cases by a large multicatalytic proteolytic particle, the proteasome. Two beta-subunits of the proteasome, LMP2 and LMP7, are inducible by interferon-gamma and alter the catalytic activities of this particle, enhancing the presentation of at least some antigens. After production of the peptide in the cytosol, it is transported across the endoplasmic reticulum (ER) membrane in an ATP-dependent manner by TAP (transporter associated with antigen presentation), a member of the ATP-binding cassette family of transport proteins. There are minor pathways for generating presented peptides directly in the ER, and some evidence suggests that peptides may be further trimmed in this location. The class I heavy chain and beta 2-microglobulin are cotranslationally translocated into the endoplasmic reticulum where their assembly may be facilitated by the sequential association of the heavy chain with chaperone proteins BiP and calnexin. The class I molecule then associates with the lumenal face of TAP where it is retained, presumably awaiting a peptide. After the class I molecule binds a peptide, it is released for exocytosis to the cell surface where cytotoxic T lymphocytes examine it for peptides derived from foreign proteins.

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=> e jondal m/au
E1            1      JONDAHL M/AU
E2            1      JONDAHL W H/AU
E3          184 -->  JONDAL M/AU
E4            1      JONDAL MARY/AU
E5            2      JONDAL MARY L/AU
E6            5      JONDAL MARY LOU/AU
E7            4      JONDAL MIKAEL/AU
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E9            62      JONDEAU G/AU
E10            4      JONDEAU GUILLAUME/AU
E11            7      JONDEAU K/AU
E12            2      JONDEAU KATAYOUN/AU

=> s e3
L75          184 "JONDAL M"/AU

=> s l75 and py=1996
        422579 PY=1996
L76            8 L75 AND PY=1996

=> d l76,ti,1-8

L76  ANSWER 1 OF 8     MEDLINE on STN
TI   External glycopeptide binding to MHC class-I in relation to expression of
     TAP transporters, beta 2-microglobulin and to pH.

L76  ANSWER 2 OF 8     MEDLINE on STN
TI   Induction of cytotoxic T-cell response by optimal-length peptides does not
     require CD4+ T-cell help.

L76  ANSWER 3 OF 8     MEDLINE on STN
TI   MHC class I-restricted CTL responses to exogenous antigens.

L76  ANSWER 4 OF 8     MEDLINE on STN
TI   Gal alpha 4Gal-binding antibodies: specificity and use for the mapping of
     glycolipids of Burkitt lymphoma and other human tumors.

L76  ANSWER 5 OF 8     MEDLINE on STN
TI   Inhibition of I-Ad-, but not Db-restricted peptide-induced thymic
     apoptosis by glucocorticoid receptor antagonist RU486 in T cell receptor
     transgenic mice.

L76  ANSWER 6 OF 8     MEDLINE on STN
TI   Bcl-2, Bax and p53 expression in B-CLL in relation to in vitro survival
     and clinical progression.

L76  ANSWER 7 OF 8     MEDLINE on STN
TI   Interleukin-10 mRNA expression in B-cell chronic lymphocytic leukaemia
     inversely correlates with progression of disease.

L76  ANSWER 8 OF 8     MEDLINE on STN
TI   Immunization with glycosylated Kb-binding peptides generates
     carbohydrate-specific, unrestricted cytotoxic T cells.


=> d l76,cbib,ab,3

L76  ANSWER 3 OF 8     MEDLINE on STN
97040549.    PubMed ID: 8885862.    MHC class I-restricted CTL responses to
     exogenous antigens. Jondal M; Schirmbeck R; Reimann J. (Microbiology and
     Tumor Biology Center, Karolinska Institute, Stockholm, Sweden. ) Immunity,
     (1996 Oct) 5 (4) 295-302.  Ref: 140. Journal code: 9432918. ISSN:
     1074-7613. Pub. country: United States. Language: English.


=> e yewdell j w/au
E1             5      YEWDALL V M/AU
E2            19      YEWDELL J/AU
E3           110 --> YEWDELL J W/AU
E4             1      YEWDELL JON W/AU
E5             4      YEWDELL JONATHAN/AU
E6            20      YEWDELL JONATHAN W/AU
E7             7      YEWE DYER M/AU
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E9            1     YEWELL JASON/AU
E10           1     YEWENG S J/AU
E11           1     YEWEY G/AU
E12           6     YEWEY G L/AU

=> s e3
L77         110 "YEWDELL J W"/AU

=> s l77 and py=1999
        458892 PY=1999
L78           8 L77 AND PY=1999

=> d l78,ti,1-8

L78  ANSWER 1 OF 8     MEDLINE on STN
TI   Mechanisms of viral interference with MHC class I antigen processing and
     presentation.

L78  ANSWER 2 OF 8     MEDLINE on STN
TI   High peptide affinity for MHC class I does not correlate with
     immunodominance.

L78  ANSWER 3 OF 8     MEDLINE on STN
TI   Intracellular localization of proteasomal degradation of a viral antigen.

L78  ANSWER 4 OF 8     MEDLINE on STN
TI   Mechanisms of exogenous antigen presentation by MHC class I molecules in
     vitro and in vivo: implications for generating CD8+ T cell responses to
     infectious agents, tumors, transplants, and vaccines.

L78  ANSWER 5 OF 8     MEDLINE on STN
TI   Modification of cysteine residues in vitro and in vivo affects the
     immunogenicity and antigenicity of major histocompatibility complex class
     I-restricted viral determinants.

L78  ANSWER 6 OF 8     MEDLINE on STN
TI   Immunodominance in major histocompatibility complex class I-restricted T
     lymphocyte responses.

L78  ANSWER 7 OF 8     MEDLINE on STN
TI   Cutting edge: adenovirus E19 has two mechanisms for affecting class I MHC
     expression.

L78  ANSWER 8 OF 8     MEDLINE on STN
TI   Spontaneous mutation at position 114 in H-2Kd affects cytotoxic T cell
     responses to influenza virus infection.


=> d l78,cbib,ab,1,2,4

L78  ANSWER 1 OF 8     MEDLINE on STN
2000078097.    PubMed ID: 10611973.   Mechanisms of viral interference with MHC
     class I antigen processing and presentation. Yewdell J W; Bennink J R.
     (Laboratory of Viral Diseases, National Institute of Allergy and
     Infectious Diseases, National Institutes of Health, Bethesda, Maryland
     20892-0440, USA.. jyewdell@nih.gov) . Annual review of cell and
     developmental biology, (1999) 15 579-606.  Ref: 87. Journal code:
     9600627. ISSN: 1081-0706. Pub. country: United States. Language: English.
AB   Viruses are ubiquitous and dangerous obligate intracellular parasites.  To
     facilitate recognition of virus-infected cells by the immune system,
     vertebrates evolved a system that displays oligopeptides derived from
     viral proteins on the surface of cells in association with class I
     molecules of the major histocompatibility complex.  Here we review the
     mechanisms counter-evolved by viruses to interfere with the generation of
     viral peptides, their intracellular trafficking, or the cell surface
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expression of class I molecules bearing viral peptides. This topic is important in its own right because the viruses that encode these proteins represent medically important pathogens, are potential vectors for vaccines or gene therapy, and provide strategies and tools for blocking immune recognition in transplantation, autoimmunity, and gene therapy. In addition, studies on viral interference provide unique insights into unfettered antigen processing and normal cellular functions that are exploited and exaggerated by viruses.

L78 ANSWER 2 OF 8 MEDLINE on STN
1999451403. PubMed ID: 10520183. High peptide affinity for MHC class I does not correlate with immunodominance. Mullbacher A; Lobigs M; **Yewdell J W**; Bennink J R; Tha Hla R; Blanden R V. (Division of Immunology and Cell Biology, John Curtin School of Medical Research, Australian National University, Canberra, A.C.T. 2601, Australia.) Scandinavian journal of immunology, **(1999 Oct)** 50 (4) 420-6. Journal code: 0323767. ISSN: 0300-9475. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cytotoxic T (Tc)-cell responses against influenza virus infection in BALB/c (H-2d) mice are dominated by Tc clones reactive to the viral nucleoprotein (NP). Here, we report investigations using recombinant vaccinia viruses (VV) encoding major histocompatibility complex (MHC) class I H-2Kd molecules differing by a single amino acid from glutamine (wild-type, Kdw) to histidine (mutant, Kdm) at position 114 located in the floor of the peptide-binding groove. Influenza-infected target cells expressing Kdw were strongly lysed by Kd-restricted Tc cells against A/WSN influenza virus or the immunodominant peptide of viral NP (NPP147-155), whereas infected Kdm-expressing targets gave little or no lysis, respectively, thus showing the immunodominance of NPP147-155. Kdm-expressing target cells saturated with synthetic NPP147-155 (10-5 M) were lysed similarly to Kdw-expressing targets by NPP147-155-specific Tc cells. Thus the defect in influenza-infected Kdm-expressing targets was quantitative; insufficient Kdm-peptide complexes were expressed. Tc-cell responses against four other viruses or alloantigens showed no effect of Kdm. When peptide transport-defective cells were infected with VV-Kdw or VV-Kdm and co-infected with a recombinant VV encoding an endoplasmic reticulum-targeted viral peptide, two influenza haemaglutinin peptides caused higher expression of Kdw than NPP147-155 indicating their higher affinity for Kdw. These results are inconsistent with the hypothesis that immunodominance in the anti-influenza response reflects high affinity of the immunodominant peptide, but are consistent with skewing of the Tc-cell receptor repertoire.

L78 ANSWER 4 OF 8 MEDLINE on STN
1999327204. PubMed ID: 10399005. Mechanisms of exogenous antigen presentation by MHC class I molecules in vitro and in vivo: implications for generating CD8+ T cell responses to infectious agents, tumors, transplants, and vaccines. **Yewdell J W**; Norbury C C; Bennink J R. (Laboratory of Viral Diseases, National Institute for Allergy and Infectious Diseases, Bethesda, Maryland 20892, USA.) Advances in immunology, **(1999)** 73 1-77. Ref: 216. Journal code: 0370425. ISSN: 0065-2776. Pub. country: United States. Language: English.

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=> e lanzavecchia a/au
E1           1      LANZAS R/AU
E2           1      LANZAT M/AU
E3         165 -->  LANZAVECCHIA A/AU
E4          21      LANZAVECCHIA ANTONIO/AU
E5          16      LANZAVECCHIA C/AU
E6          31      LANZAVECCHIA G/AU
E7           2      LANZAVECCHIA GIULIO/AU
E8           1      LANZAVECCHIA L/AU
E9           1      LANZAVECCHIA P/AU
E10          2      LANZAVECCHIA P JR/AU
E11         18      LANZAVECCHIA S/AU
E12          5      LANZAVECCHIA SALVATORE/AU
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=> s e3
L79          165 "LANZAVECCHIA A"/AU

=> s l79 and py=1996
        422579 PY=1996
L80            6 L79 AND PY=1996

=> d l80,ti,1-6

L80  ANSWER 1 OF 6     MEDLINE on STN
TI   Restricted TCR repertoire and long-term persistence of donor-derived
     antigen-experienced CD4+ T cells in allogeneic bone marrow transplantation
     recipients.

L80  ANSWER 2 OF 6     MEDLINE on STN
TI   Mechanisms of antigen uptake for presentation.

L80  ANSWER 3 OF 6     MEDLINE on STN
TI   Signal extinction and T cell repolarization in T helper
     cell-antigen-presenting cell conjugates.

L80  ANSWER 4 OF 6     MEDLINE on STN
TI   Ligation of CD40 on dendritic cells triggers production of high levels of
     interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC
     activation.

L80  ANSWER 5 OF 6     MEDLINE on STN
TI   Different responses are elicited in cytotoxic T lymphocytes by different
     levels of T cell receptor occupancy.

L80  ANSWER 6 OF 6     MEDLINE on STN
TI   T cell activation determined by T cell receptor number and tunable
     thresholds.


=> d l80,cbib,ab,2,5,6

L80  ANSWER 2 OF 6     MEDLINE on STN
96415587.    PubMed ID: 8794000.   Mechanisms of antigen uptake for
     presentation. Lanzavecchia A. (Basel Institute for Immunology,
     Switzerland.. LANZAVECCHIA@bii.ch) . Current opinion in immunology, (1996
     Jun) 8 (3) 348-54.  Ref: 93. Journal code: 8900118. ISSN: 0952-7915. Pub.
     country: ENGLAND: United Kingdom. Language: English.
AB   There is growing evidence that different antigen-presenting cells use
     specialized mechanisms for antigen uptake.  Macropinocytosis and the
     activity of the mannose receptor have been identified as efficient
     mechanisms of antigen capture in dendritic cells.  The mechanism of uptake
     determines the intracellular compartment to which antigen is delivered and
     may determine the type of T-cell epitopes generated.  New pathways for
     presentation of exogenous antigens on MHC class I and II molecules have
     been identified.  These findings provide new insights into antigen
     presentation in vivo and will be instrumental in designing better methods
     of vaccination.

L80  ANSWER 5 OF 6     MEDLINE on STN
96298953.    PubMed ID: 8666949.   Different responses are elicited in
     cytotoxic T lymphocytes by different levels of T cell receptor occupancy.
     Valitutti S; Muller S; Dessing M; Lanzavecchia A. (Basel Institute for
     Immunology, Switzerland. ) Journal of experimental medicine, (1996 Apr
     1) 183 (4) 1917-21.  Journal code: 2985109R. ISSN: 0022-1007. Pub.
     country: United States. Language: English.
AB   We have investigated the level of TCR occupancy required to elicit
     different biological responses in human CTL clones specific for an
     influenza matrix peptide.  Specific cytotoxicity could be detected at
     extremely low peptide concentrations (10(-12) to 10(-15) M).  However,
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only at peptide concentrations > 10(-9) M, while autonomous proliferation required even higher peptide concentrations. In parallel experiments we measured TCR downregulation to estimate the number of TCRs triggered. We observed that at low peptide concentrations, where only cytotoxicity is triggered, TCR downregulation was hardly detectable. Conversely, induction of IFN-gamma production and proliferation required triggering of at least 20-50% of TCRs. Taken together these results indicate that a single CTL can graduate different biological responses as a function of antigen concentration and that killing of the specific target does not necessarily result in full activation.

L80 ANSWER 6 OF 6 MEDLINE on STN
96275593. PubMed ID: 8658175. T cell activation determined by T cell receptor number and tunable thresholds. Viola A; **Lanzavecchia A.** (Basel Institute for Immunology, Switzerland.) Science, **(1996 Jul 5)** 273 (5271) 104-6. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The requirements for T cell activation have been reported to vary widely depending on the state of the T cell, the type of antigen-presenting cell, and the nature of the T cell receptor (TCR) ligand. A unitary requirement for T cell responses was revealed by measurement of the number of triggered TCRs. Irrespective of the nature of the triggering ligand, T cells "counted" the number of triggered TCRs and responded when a threshold of approximately 8000 TCRs was reached. The capacity to reach the activation threshold was severely compromised by a reduction in the number of TCRs. Costimulatory signals lowered the activation threshold to approximately 1500 TCRs, thus making T cells more sensitive to antigenic stimulation.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
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L16          6 S L15 NOT L10
               E HEARD J/IN
L17          2 S E8
L18          2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
               E SCHWARTZ O/AU
L19         10 S E7
L20         90 S E3
L21          2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
               E BUSEYNE F/AU
L22         25 S E3 OR E4
L23         21 S L22 NOT L20
               E MARSAC E/AU
L24          1 S E2
L25          0 S L24 NOT L20
               E RIVIERE Y/AU
L26        104 S E3 OR E4
L27        101 S L26 NOT L20
               E HEARD J M/AU
L28          7 S E8
L29          7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
               E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30       2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31       1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32        795 S L31 AND EXOGENOUS
L33        790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34         77 S L33 AND PLASMID/CLM
L35         11 S L34 AND PY<2002
L36         49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37        138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38         10 S L37 AND DENDRITIC
L39          1 S L38 AND (GENE VACCINATION)
L40        181 S (NAKED PLASMID DNA)
L41         11 S L40 AND PY=1996
L42          5 S L40 AND DENDRITIC
L43          0 S L40 AND (MULTIVALENT)
L44         80 S MULTIVALENT VACCINE
L45          1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46        162 S MULTIVALEN? VACCIN?
L47          6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48          0 S L46 AND (TWO PLASMIDS)
L49          1 S (MULTI-PLASMID DNA VACCINATION)
L50     140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51       7795 S L50 AND VACCIN?
L52        324 S L51 AND (PLASMID?)
L53        324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54        132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55       4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56       1102 S L55 AND VACCIN?
L57         70 S L56 AND PLASMID?
L58         25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59          3 S L58 NOT L54
L60         22 S L58 NOT L59
L61        203 S (IN VIVO GENE DELIVERY)
L62          1 S L61 AND (STABLE TRANSDUCTION)
               E WHITT M A/AU
L63         25 S E3
L64          1 S L63 AND PY=1990
               E AMARA R R/AU
L65          7 S E3
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                 E BUSEYNE F/AU
L67           22 S E3
L68            6 S L67 AND PY=2001
L69            2 S L68 AND VIRION
                 E NALDINI L/AU
L70           60 S E3
L71            3 S L70 AND PY=1996
L72            2 S L70 AND PY=1997
                 E ROCK K L/AU
L73          112 S E3
L74            7 S L73 AND PY=1996
                 E JONDAL M/AU
L75          184 S E3
L76            8 S L75 AND PY=1996
                 E YEWDELL J W/AU
L77          110 S E3
L78            8 S L77 AND PY=1999
                 E LANZAVECCHIA A/AU
L79          165 S E3
L80            6 S L79 AND PY=1996

=> s l73 and py=1999
        458892 PY=1999
L81            5 L73 AND PY=1999

=> d l81,ti,1-5

L81  ANSWER 1 OF 5     MEDLINE on STN
TI   Proteolysis and class I major histocompatibility complex antigen
     presentation.

L81  ANSWER 2 OF 5     MEDLINE on STN
TI   A monoclonal antibody reactive with a 40-kDa molecule on fetal thymocytes
     and tumor cells blocks proliferation and stimulates aggregation and
     apoptosis.

L81  ANSWER 3 OF 5     MEDLINE on STN
TI   Degradation of cell proteins and the generation of MHC class I-presented
     peptides.

L81  ANSWER 4 OF 5     MEDLINE on STN
TI   Class II antigen processing defects in two H2d mouse cell lines are caused
     by point mutations in the H2-DMa gene.

L81  ANSWER 5 OF 5     MEDLINE on STN
TI   Cytotoxic T-cell immunity to virus-infected non-haematopoietic cells
     requires presentation of exogenous antigen.


=> d l81,cbib,ab,5

L81  ANSWER 5 OF 5     MEDLINE on STN
1999176419.    PubMed ID: 10078533.   Cytotoxic T-cell immunity to
     virus-infected non-haematopoietic cells requires presentation of exogenous
     antigen. Sigal L J; Crotty S; Andino R; Rock K L. (Department of
     Pathology, University of Massachusetts Medical Center, Worcester
     01655-0118, USA. ) Nature, (1999 Mar 4) 398 (6722) 77-80.  Journal code:
     0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language:
     English.
AB   Cytotoxic T lymphocytes (CTLs) are thought to detect viral infections by
     monitoring the surface of all cells for the presence of viral peptides
     bound to major histocompatibility complex (MHC) class I molecules.  In
     most cells, peptides presented by MHC class I molecules are derived
     exclusively from proteins synthesized by the antigen-bearing cells.
     Macrophages and dendritic cells also have an alternative MHC class I
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pathway that can present peptides derived from extracellular antigens;
however, the physiological role of this process is unclear.  Here we show
that virally infected non-haematopoietic cells are unable to stimulate
primary CTL-mediated immunity directly.  Instead, bone-marrow-derived
cells are required as antigen-presenting cells (APCs) to initiate
anti-viral CTL responses.  In these APCs, the alternative (exogenous) MHC
class I pathway is the obligatory mechanism for the initiation of CTL
responses to viruses that infect only non-haematopoietic cells.


=> e reimann j/au
E1            2      REIMANN ILSELORE R/AU
E2            1      REIMANN IRIS/AU
E3          177 --> REIMANN J/AU
E4            8      REIMANN J D/AU
E5            2      REIMANN J E/AU
E6            2      REIMANN J F/AU
E7            1      REIMANN J O/AU
E8            1      REIMANN JAMES D/AU
E9            1      REIMANN JASINSKI D/AU
E10           6      REIMANN JENS/AU
E11           1      REIMANN JOACHIM O/AU
E12           2      REIMANN JOACHIM O F/AU

=> s e3
L82         177 "REIMANN J"/AU

=> s l82 and py=1999
       458892 PY=1999
L83          12 L82 AND PY=1999

=> d l83,ti,1-12

L83  ANSWER 1 OF 12     MEDLINE on STN
TI   Alternative pathways for processing exogenous and endogenous antigens that
     can generate peptides for MHC class I-restricted presentation.

L83  ANSWER 2 OF 12     MEDLINE on STN
TI   Malabsorption with progressive weight loss and multiple intestinal ulcers
     in a patient with T-cell lymphoma.

L83  ANSWER 3 OF 12     MEDLINE on STN
TI   Priming MHC-I-restricted cytotoxic T lymphocyte responses to exogenous
     hepatitis B surface antigen is CD4+ T cell dependent.

L83  ANSWER 4 OF 12     MEDLINE on STN
TI   Adjuvants that enhance priming of cytotoxic T cells to a Kb-restricted
     epitope processed from exogenous but not endogenous hepatitis B surface
     antigen.

L83  ANSWER 5 OF 12     MEDLINE on STN
TI   Purification and characterization of hepatitis B virus surface antigen
     particles produced in Drosophila Schneider-2 cells.

L83  ANSWER 6 OF 12     MEDLINE on STN
TI   Tumour necrosis factor-alpha (TNF-alpha) transcription and translation in
     the CD4+ T cell-transplanted scid mouse model of colitis.

L83  ANSWER 7 OF 12     MEDLINE on STN
TI   Truncated or chimeric endogenous protein antigens gain immunogenicity for
     B cells by stress protein-facilitated expression.

L83  ANSWER 8 OF 12     MEDLINE on STN
TI   Immunostimulatory CpG motifs trigger a T helper-1 immune response to human
     immunodeficiency virus type-1 (HIV-1) gp 160 envelope proteins.
```

TI Enhancing the immunogenicity of exogenous hepatitis B surface antigen-based vaccines for MHC-I-restricted T cells.

L83 ANSWER 10 OF 12 MEDLINE on STN
TI Colitis-inducing potency of CD4+ T cells in immunodeficient, adoptive hosts depends on their state of activation, IL-12 responsiveness, and CD45RB surface phenotype.

L83 ANSWER 11 OF 12 MEDLINE on STN
TI DNA immunization confers systemic, but not mucosal, protection against enteroinvasive bacteria.

L83 ANSWER 12 OF 12 MEDLINE on STN
TI Immunization of woodchucks with plasmids expressing woodchuck hepatitis virus (WHV) core antigen and surface antigen suppresses WHV infection.

=> d l83,cbib,ab,1

L83 ANSWER 1 OF 12 MEDLINE on STN
2000097561. PubMed ID: 10631943. Alternative pathways for processing exogenous and endogenous antigens that can generate peptides for MHC class I-restricted presentation. **Reimann J**; Schirmbeck R. (Department of Medical Microbiology and Immunology, University of Ulm, Germany.. joerg.reimann@medizin.uni-ulm.de) . Immunological reviews, **(1999 Dec)** 172 131-52. Ref: 198. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.
AB The concept of distinct endogenous and exogenous pathways for generating peptides for MHC-I and MHC-II-restricted presentation to CD4+ or CD8+ T cells fits well with the bulk of experimental data. Nevertheless, evidence is emerging for alternative processing pathways that generate peptides for MHC-I-restricted presentation. Using a well characterized, particulate viral antigen of prominent medical importance (the hepatitis B surface antigen), we summarize our evidence that the efficient, endolysosomal processing of exogenous antigens can lead to peptide-loaded MHC-I molecules. In addition, we describe evidence for endolysosomal processing of mutant, stress protein-bound, endogenous antigens that liberate peptides binding to (and presented by) MHC-I molecules. The putative biological role of alternative processing of antigens generating cytotoxic T-lymphocyte-stimulating epitopes is discussed.

=> e brander c/au

E1	1	BRANDER ANTTI/AU
E2	1	BRANDER B/AU
E3	37 -->	BRANDER C/AU
E4	12	BRANDER CHRISTIAN/AU
E5	1	BRANDER DITTE C/AU
E6	47	BRANDER E/AU
E7	2	BRANDER E E/AU
E8	1	BRANDER F/AU
E9	8	BRANDER G/AU
E10	19	BRANDER G C/AU
E11	4	BRANDER J/AU
E12	1	BRANDER J A/AU

=> s e3
L84 37 "BRANDER C"/AU

=> s l84 and py=1999
458892 PY=1999
L85 3 L84 AND PY=1999

=> d l85,ti,1-3

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TI   Efficient processing of the immunodominant, HLA-A*0201-restricted human
     immunodeficiency virus type 1 cytotoxic T-lymphocyte epitope despite
     multiple variations in the epitope flanking sequences.

L85  ANSWER 2 OF 3     MEDLINE on STN
TI   T lymphocyte responses in HIV-1 infection: implications for vaccine
     development.

L85  ANSWER 3 OF 3     MEDLINE on STN
TI   Persistent HIV-1-specific CTL clonal expansion despite high viral burden
     post in utero HIV-1 infection.


=> d l85,cbib,ab,2

L85  ANSWER 2 OF 3     MEDLINE on STN
1999379880.    PubMed ID: 10448136.    T lymphocyte responses in HIV-1
     infection: implications for vaccine development. Brander C; Walker B D.
     (Partners AIDS Research Center, Massachusetts General Hospital, Harvard
     Medical School, MGH-East, 5th floor, 149 13th Street, Charlestown, MA
     02129, USA.. brander@helix.mgh.harvard.edu) . Current opinion in
     immunology, (1999 Aug) 11 (4) 451-9.  Ref: 106. Journal code: 8900118.
     ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.
AB   Substantial progress has been made over the past year in understanding the
     cellular immune response in HIV pathogenesis.  Cytotoxic T lymphocytes
     play a critical role in establishing the level of viremia and
     virus-specific Th cell responses appear to affect the in vivo efficacy of
     cytotoxic T lymphocytes.  Together, these new data provide important
     insights to refocus efforts aimed at immunotherapeutic interventions and
     vaccine development.


=> e condon c/au
E1            2      CONDON B S/AU
E2            1      CONDON BARRIE/AU
E3           29 --> CONDON C/AU
E4            4      CONDON C A/AU
E5            2      CONDON C D/AU
E6            2      CONDON C F/AU
E7           11      CONDON C J/AU
E8            1      CONDON C M/AU
E9            2      CONDON C W/AU
E10           6      CONDON CIARAN/AU
E11           4      CONDON D/AU
E12           2      CONDON D J/AU

=> s e3
L86          29 "CONDON C"/AU

=> s l86 and py=1996
        422579 PY=1996
L87           3 L86 AND PY=1996

=> d l87,ti,1-3

L87  ANSWER 1 OF 3     MEDLINE on STN
TI   Aminoacyl-tRNA synthetase gene regulation in Bacillus subtilis.

L87  ANSWER 2 OF 3     MEDLINE on STN
TI   DNA-based immunization by in vivo transfection of dendritic cells.

L87  ANSWER 3 OF 3     MEDLINE on STN
TI   Processing of the leader mRNA plays a major role in the induction of thrS
     expression following threonine starvation in Bacillus subtilis.
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=> d l87,cbib,ab,2

L87  ANSWER 2 OF 3     MEDLINE on STN
96434687.    PubMed ID: 8837611.   DNA-based immunization by in vivo
     transfection of dendritic cells. Condon C; Watkins S C; Celluzzi C M;
     Thompson K; Falo L D Jr. (Department of Dermatology, University of
     Pittsburgh School of Medicine, Pennsylvania 15213, USA. ) Nature medicine,
     (1996 Oct) 2 (10) 1122-8.  Journal code: 9502015. ISSN: 1078-8956. Pub.
     country: United States. Language: English.
AB   Delivery of antigen in a manner that induces effective, antigen-specific
     immunity is a critical challenge in vaccine design.  Optimal antigen
     presentation is mediated by professional antigen-presenting cells (APCs)
     capable of taking up, processing and presenting antigen to T cells in the
     context of costimulatory signals required for T-cell activation.
     Developing immunization strategies to optimize antigen presentation by
     dendritic cells, the most potent APCs, is a rational approach to vaccine
     design.  Here we show that cutaneous genetic immunization with naked DNA
     results in potent, antigen-specific, cytotoxic T lymphocyte-mediated
     protective tumor immunity.  This method of immunization results in the
     transfection of skin-derived dendritic cells, which localize in the
     draining lymph nodes.  These observations provide a basis for further
     development of DNA-based vaccines and demonstrate the feasibility of
     genetically engineering dendritic cells in vivo.


=> e corr m/au
E1           16      CORR L/AU
E2            7      CORR L A/AU
E3           32 --> CORR M/AU
E4            1      CORR M J/AU
E5            1      CORR M P/AU
E6            1      CORR M T/AU
E7           13      CORR MARIPAT/AU
E8            1      CORR MELISSA J/AU
E9            1      CORR MENGUY FABIENNE/AU
E10           3      CORR N/AU
E11          46      CORR P/AU
E12         117      CORR P B/AU

=> s e3
L88          32 "CORR M"/AU

=> s l88 and py=1996
         422579 PY=1996
L89           3 L88 AND PY=1996

=> d l89,ti,1-3

L89  ANSWER 1 OF 3     MEDLINE on STN
TI   Gene vaccination with naked plasmid DNA: mechanism of CTL priming.

L89  ANSWER 2 OF 3     MEDLINE on STN
TI   Immunostimulatory DNA sequences necessary for effective intradermal gene
     immunization.

L89  ANSWER 3 OF 3     MEDLINE on STN
TI   Preferential induction of a Th1 immune response and inhibition of specific
     IgE antibody formation by plasmid DNA immunization.


=> d l89,cbib,ab

L89  ANSWER 1 OF 3     MEDLINE on STN
97033532.    PubMed ID: 8879229.   Gene vaccination with naked plasmid DNA:
     mechanism of CTL priming. Corr M; Lee D J; Carson D A; Tighe H.
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92093-0663, USA.) Journal of experimental medicine, **(1996 Oct 1)** 184 (4) 1555-60. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The injection of naked plasmid DNA directly into the muscle cells of mice has been shown to induce potent humoral and cellular immune responses. The generation of a cytotoxic T lymphocyte (CTL) response after plasmid DNA injection may involve the presentation of the expressed antigen in the context of the injected myocytes' endogenous major histocompatibility (MHC)-encoded class I molecules or may use the MHC molecules of bone marrow-derived antigen presenting cells (APC) which are capable of providing co-stimulation as well. To resolve which cell type provides the specific restricting element for this method of vaccination we generated parent-->F1 bone marrow chimeras in which H-2bxd recipient mice received bone marrow that expressed only H-2b or H-2d MHC molecules. These mice were injected intramuscularly with naked plasmid DNA that encoded the nucleoprotein from the A/PR/8/34 influenza strain, which as a single antigen has epitopes for both H-2Db and H-2Kd. The resulting CTL responses were restricted to the MHC haplotype of the bone marrow alone and not to the second haplotype expressed by the recipient's myocytes. The role of somatic tissues that express protein from injected plasmids may be to serve as a reservoir for that antigen which is then transferred to the APC. Consequently, our data show that the mechanism of priming in this novel method for vaccination uses the MHC from bone marrow-derived APC, which are efficient at providing all of the necessary signals for priming the T cell.

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=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
L6            2 S E3
L7            1 S L6 NOT L1
                E HEARD JEAN MICHEL/IN
L8            6 S E3
L9            5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
                E SCHWARTZ O/IN
L10          16 S E3-E5
                E BUSEYNE F/IN
L11           1 S E3
L12           0 S L11 NOT L10
                E MARSAC D/IN
L13           2 S E3
L14           1 S L13 NOT L10
                E RIVIERE Y/IN
L15           7 S E3 OR E4
L16           6 S L15 NOT L10
                E HEARD J/IN
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L18              2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                   E SCHWARTZ O/AU
L19             10 S E7
L20             90 S E3
L21              2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                   E BUSEYNE F/AU
L22             25 S E3 OR E4
L23             21 S L22 NOT L20
                   E MARSAC E/AU
L24              1 S E2
L25              0 S L24 NOT L20
                   E RIVIERE Y/AU
L26            104 S E3 OR E4
L27            101 S L26 NOT L20
                   E HEARD J M/AU
L28              7 S E8
L29              7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                   E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30           2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31           1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32            795 S L31 AND EXOGENOUS
L33            790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34             77 S L33 AND PLASMID/CLM
L35             11 S L34 AND PY<2002
L36             49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37            138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38             10 S L37 AND DENDRITIC
L39              1 S L38 AND (GENE VACCINATION)
L40            181 S (NAKED PLASMID DNA)
L41             11 S L40 AND PY=1996
L42              5 S L40 AND DENDRITIC
L43              0 S L40 AND (MULTIVALENT)
L44             80 S MULTIVALENT VACCINE
L45              1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46            162 S MULTIVALEN? VACCIN?
L47              6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48              0 S L46 AND (TWO PLASMIDS)
L49              1 S (MULTI-PLASMID DNA VACCINATION)
L50         140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L51           7795 S L50 AND VACCIN?
L52            324 S L51 AND (PLASMID?)
L53            324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54            132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55           4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56           1102 S L55 AND VACCIN?
L57             70 S L56 AND PLASMID?
L58             25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59              3 S L58 NOT L54
L60             22 S L58 NOT L59
L61            203 S (IN VIVO GENE DELIVERY)
L62              1 S L61 AND (STABLE TRANSDUCTION)
                   E WHITT M A/AU
L63             25 S E3
L64              1 S L63 AND PY=1990
                   E AMARA R R/AU
L65              7 S E3
L66              2 S L65 AND PY=2001
                   E BUSEYNE F/AU
L67             22 S E3
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L69            2 S L68 AND VIRION
                 E NALDINI L/AU
L70           60 S E3
L71            3 S L70 AND PY=1996
L72            2 S L70 AND PY=1997
                 E ROCK K L/AU
L73          112 S E3
L74            7 S L73 AND PY=1996
                 E JONDAL M/AU
L75          184 S E3
L76            8 S L75 AND PY=1996
                 E YEWDELL J W/AU
L77          110 S E3
L78            8 S L77 AND PY=1999
                 E LANZAVECCHIA A/AU
L79          165 S E3
L80            6 S L79 AND PY=1996
L81            5 S L73 AND PY=1999
                 E REIMANN J/AU
L82          177 S E3
L83           12 S L82 AND PY=1999
                 E BRANDER C/AU
L84           37 S E3
L85            3 S L84 AND PY=1999
                 E CONDON C/AU
L86           29 S E3
L87            3 S L86 AND PY=1996
                 E CORR M/AU
L88           32 S E3
L89            3 S L88 AND PY=1996

=> s l88 and py=1999
        458892 PY=1999
L90            4 L88 AND PY=1999

=> d l90,ti,1-4

L90  ANSWER 1 OF 4     MEDLINE on STN
TI   In vivo priming by DNA injection occurs predominantly by antigen transfer.

L90  ANSWER 2 OF 4     MEDLINE on STN
TI   Human rheumatoid factor production is dependent on CD40 signaling and
     autoantigen.

L90  ANSWER 3 OF 4     MEDLINE on STN
TI   DNA vaccination against multiple myeloma.

L90  ANSWER 4 OF 4     MEDLINE on STN
TI   Rheumatoid factor B cell tolerance via autonomous Fas/FasL-independent
     apoptosis.


=> d l90,cbib,ab

L90  ANSWER 1 OF 4     MEDLINE on STN
1999458926.    PubMed ID: 10528170.   In vivo priming by DNA injection occurs
     predominantly by antigen transfer. Corr M; von Damm A; Lee D J; Tighe H.
     (Department of Medicine, The Sam and Rose Stein Institute for Research on
     Aging, University of California at San Diego, La Jolla 92093, USA..
     mcorr@ucsd.edu) . Journal of immunology (Baltimore, Md. : 1950), (1999
     Nov 1) 163 (9) 4721-7.  Journal code: 2985117R. ISSN: 0022-1767. Pub.
     country: United States. Language: English.
AB   DNA vaccines can stimulate both humoral and cytolytic immune responses.
     Although bone marrow-derived elements present the expressed Ag, the
     mechanisms for acquiring immunogenic peptides have yet to be fully
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process extracellular proteins produced by other transfected cells. Using a transactivating plasmid system and bone marrow chimeras, we show that both mechanisms appear to be involved; however, the bulk of the immune response is dependent on expression of Ag by nonlymphoid tissues and transfer to APCs. These in vivo studies are the first to define the role of transfected nonlymphoid cells in generating Ag for presentation by bone marrow-derived APCs after needle injection with plasmid DNA.

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=> deliyannis g/au
DELIYANNIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> e deliyannis g/au
E1            4      DELIYANNIS A A/AU
E2            1      DELIYANNIS E/AU
E3            6 --> DELIYANNIS G/AU
E4            4      DELIYANNIS G A/AU
E5            3      DELIYANNIS GEORGIA/AU
E6            2      DELIYANNIS S N/AU
E7            2      DELIYANNIS T/AU
E8            1      DELIYANNIS T D/AU
E9            3      DELIYIANNI V/AU
E10           1      DELIYIANNIS E/AU
E11           4      DELIYIANNIS S/AU
E12           1      DELIYIANNIS S J/AU

=> s e3
L91           6 "DELIYANNIS G"/AU

=> s l91 and py=2000
        486339 PY=2000
L92           2 L91 AND PY=2000

=> d l92,cbib,ab,1-2
```

L92 ANSWER 1 OF 2 MEDLINE on STN
2000300960. PubMed ID: 10823919. A fusion DNA vaccine that targets antigen-presenting cells increases protection from viral challenge. **Deliyannis G**; Boyle J S; Brady J L; Brown L E; Lew A M. (Cooperative Research Center for Vaccine Technology, Department of Microbiology and Immunology, University of Melbourne, Melbourne 3052, Australia.) Proceedings of the National Academy of Sciences of the United States of America, **(2000 Jun 6)** 97 (12) 6676-80. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Improving the immunological potency, particularly the Ab response, is a serious hurdle for the protective efficacy and hence broad application of DNA vaccines. We examined the immunogenicity and protective efficacy of a hemagglutinin-based influenza DNA vaccine that was targeted to antigen-presenting cells (APCs) by fusion to CTLA4. The targeted vaccine was shown to induce an accelerated and increased Ab response (as compared with those receiving the nontargeted control) that was predominated by IgG1 and recognized conformationally dependent viral epitopes. Moreover, mice receiving the APC-targeted DNA vaccine had significantly reduced viral titers (100-fold) after a nonlethal virus challenge. The increased protective efficacy was most likely because of increased Ab responses, as cytotoxic T lymphocyte responses were not enhanced. Targeting was demonstrated by direct binding studies of CTLA4 fusion proteins to the cognate ligand (B7; expressed on APCs in vivo). In addition, a targeted protein was detected at 4-fold higher levels in draining lymph nodes within 2-24 h of administration. Therefore, this study demonstrates that targeting DNA-encoded antigen to APCs results in enhanced immunity and strongly suggests that this approach may be useful in improving the

protective efficacy of DNA vaccines.

L92 ANSWER 2 OF 2 MEDLINE on STN
2000135872. PubMed ID: 10671225. Effect of pre-existing cytotoxic T lymphocytes on therapeutic vaccines. Sherritt M A; Gardner J; Elliott S L; Schmidt C; Purdie D; **Deliyannis G**; Heath W R; Suhrbier A. (Australian National Centre for International & Tropical Health & Nutrition, Queensland Institute of Medical Research and the University of Queensland, Royal Brisbane Hospital, Brisbane, Australia.) European journal of immunology, **(2000 Feb)** 30 (2) 671-7. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Therapeutic vaccines which aim to induce CD8(+) cytotoxic T lymphocyte (CTL) responses will often be required to perform in the presence of pre-existing CTL which recognize epitopes within the vaccine. Here we explore the ability of a viral vaccine vector presenting several co-dominant CTL epitopes to prime CTL responses in animals that have a pre-existing CTL response to one of the epitopes in the vaccine. The vaccine was usually capable of inducing multiple new responses, suggesting that immunodomination effects of pre-existing CTL may generally be minimal following vaccination. However, when large numbers of pre-existing CTL were present, a novel type of immune modulation was observed whereby (1) the vaccine failed to prime efficiently new CTL responses that were restricted by the same MHC gene as the pre-existing responses, and (2) vaccine-induced CTL responses restricted by other MHC genes were enhanced. These results may have implications for therapeutic multi-epitope vaccines for diseases like HIV and melanoma, which aim to broaden CTL responses.

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=> d h is
'H' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
'IS' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and
PY.

To display a particular field or fields,  enter the display field
codes.  For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>).  Examples of formats include: 'BIB';
'AB'; 'SO,ST'.  You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be
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used with the DISPLAY ACC command to display the record for a
specified Accession Number.
ENTER DISPLAY FORMAT (BIB):d his
'D' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
'HIS' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and
PY.

To display a particular field or fields,  enter the display field
codes.  For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>).  Examples of formats include: 'BIB';
'AB'; 'SO,ST'.  You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be
used with the DISPLAY ACC command to display the record for a
specified Accession Number.
ENTER DISPLAY FORMAT (BIB):ti

L92  ANSWER 1 OF 2     MEDLINE on STN
TI   A fusion DNA vaccine that targets antigen-presenting cells increases
     protection from viral challenge.


=> d his

     (FILE 'HOME' ENTERED AT 16:18:51 ON 29 APR 2004)

     FILE 'USPATFULL' ENTERED AT 16:19:01 ON 29 APR 2004
                E SCHWARTZ OLIVIER/IN
L1            2 S E3

     FILE 'WPIDS' ENTERED AT 16:21:29 ON 29 APR 2004

     FILE 'USPATFULL' ENTERED AT 16:21:37 ON 29 APR 2004
                E BUSEYNE FLORENCE/IN
L2            1 S E3
L3            0 S L2 NOT L1
                E MARSAC DELPHINE/IN
L4            1 S E3
L5            0 S L4 NOT L1
                E RIVIERE YVES/IN
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L7              1 S L6 NOT L1
                  E HEARD JEAN MICHEL/IN
L8              6 S E3
L9              5 S L8 NOT L1

     FILE 'WPIDS' ENTERED AT 16:24:12 ON 29 APR 2004
                  E SCHWARTZ OLIVIER/IN
                  E SCHWARTZ O/IN
L10            16 S E3-E5
                  E BUSEYNE F/IN
L11             1 S E3
L12             0 S L11 NOT L10
                  E MARSAC D/IN
L13             2 S E3
L14             1 S L13 NOT L10
                  E RIVIERE Y/IN
L15             7 S E3 OR E4
L16             6 S L15 NOT L10
                  E HEARD J/IN
L17             2 S E8
L18             2 S L17 NOT L10

     FILE 'MEDLINE' ENTERED AT 16:30:22 ON 29 APR 2004
                  E SCHWARTZ O/AU
L19            10 S E7
L20            90 S E3
L21             2 S L20 AND (DNA IMMUN? OR DNA VACCIN? OR GENE VACCIN? OR DNA-BAS
                  E BUSEYNE F/AU
L22            25 S E3 OR E4
L23            21 S L22 NOT L20
                  E MARSAC E/AU
L24             1 S E2
L25             0 S L24 NOT L20
                  E RIVIERE Y/AU
L26           104 S E3 OR E4
L27           101 S L26 NOT L20
                  E HEARD J M/AU
L28             7 S E8
L29             7 S L28 NOT L20

     FILE 'USPATFULL' ENTERED AT 16:52:37 ON 29 APR 2004
                  E (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L30          2648 S (DNA IMMUN? OR DNA INJECTION OR DNA-BASED IMMUN? OR DNA-BASED
L31          1140 S L30 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR MHC CLASS I OR MHC
L32           795 S L31 AND EXOGENOUS
L33           790 S L32 AND (DNA IMMUN?/CLM OR DNA INJECTION/CLM OR DNA-BASED IMM
L34            77 S L33 AND PLASMID/CLM
L35            11 S L34 AND PY<2002
L36            49 S L34 AND AY<2002

     FILE 'MEDLINE' ENTERED AT 17:06:55 ON 29 APR 2004
L37           138 S (DNA-BASED IMMUNIZATION OR GENE VACCINATION)
L38            10 S L37 AND DENDRITIC
L39             1 S L38 AND (GENE VACCINATION)
L40           181 S (NAKED PLASMID DNA)
L41            11 S L40 AND PY=1996
L42             5 S L40 AND DENDRITIC
L43             0 S L40 AND (MULTIVALENT)
L44            80 S MULTIVALENT VACCINE
L45             1 S L44 AND (GENETIC IMMUNIZATION OR DNA IMMUNIZATION OR DNA-BASE
L46           162 S MULTIVALEN? VACCIN?
L47             6 S L46 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L48             0 S L46 AND (TWO PLASMIDS)
L49             1 S (MULTI-PLASMID DNA VACCINATION)
L50        140917 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
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L52          324 S L51 AND (PLASMID?)
L53          324 S L52 AND (POLYNUCLEOTIDE OR DNA OR PLASMID? OR DNA-BASED OR NA
L54          132 S L53 AND (CTL OR CYTOTOXIC OR CLASS I)
L55         4028 S (SIV OR SIMIAN IMMUNODEFICIENCY VIRUS)
L56         1102 S L55 AND VACCIN?
L57           70 S L56 AND PLASMID?
L58           25 S L57 AND (CTL OR CYTOTOXIC OR CLASS I)
L59            3 S L58 NOT L54
L60           22 S L58 NOT L59
L61          203 S (IN VIVO GENE DELIVERY)
L62            1 S L61 AND (STABLE TRANSDUCTION)
                 E WHITT M A/AU
L63           25 S E3
L64            1 S L63 AND PY=1990
                 E AMARA R R/AU
L65            7 S E3
L66            2 S L65 AND PY=2001
                 E BUSEYNE F/AU
L67           22 S E3
L68            6 S L67 AND PY=2001
L69            2 S L68 AND VIRION
                 E NALDINI L/AU
L70           60 S E3
L71            3 S L70 AND PY=1996
L72            2 S L70 AND PY=1997
                 E ROCK K L/AU
L73          112 S E3
L74            7 S L73 AND PY=1996
                 E JONDAL M/AU
L75          184 S E3
L76            8 S L75 AND PY=1996
                 E YEWDELL J W/AU
L77          110 S E3
L78            8 S L77 AND PY=1999
                 E LANZAVECCHIA A/AU
L79          165 S E3
L80            6 S L79 AND PY=1996
L81            5 S L73 AND PY=1999
                 E REIMANN J/AU
L82          177 S E3
L83           12 S L82 AND PY=1999
                 E BRANDER C/AU
L84           37 S E3
L85            3 S L84 AND PY=1999
                 E CONDON C/AU
L86           29 S E3
L87            3 S L86 AND PY=1996
                 E CORR M/AU
L88           32 S E3
L89            3 S L88 AND PY=1996
L90            4 S L88 AND PY=1999
                 E DELIYANNIS G/AU
L91            6 S E3
L92            2 S L91 AND PY=2000

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 20:11:43 ON 29 APR 2004
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